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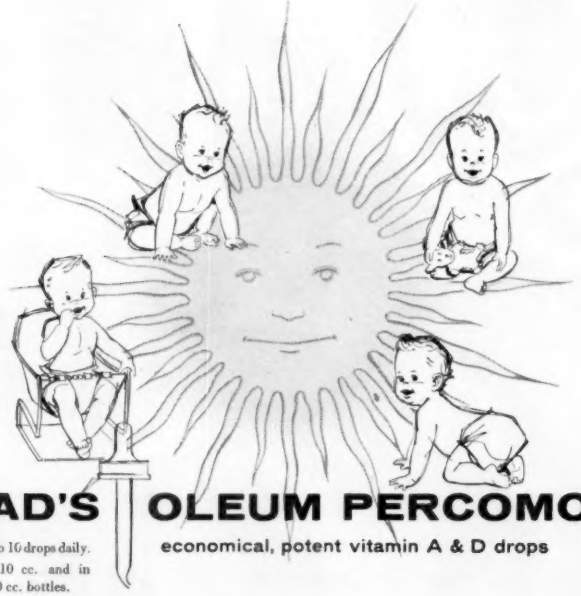

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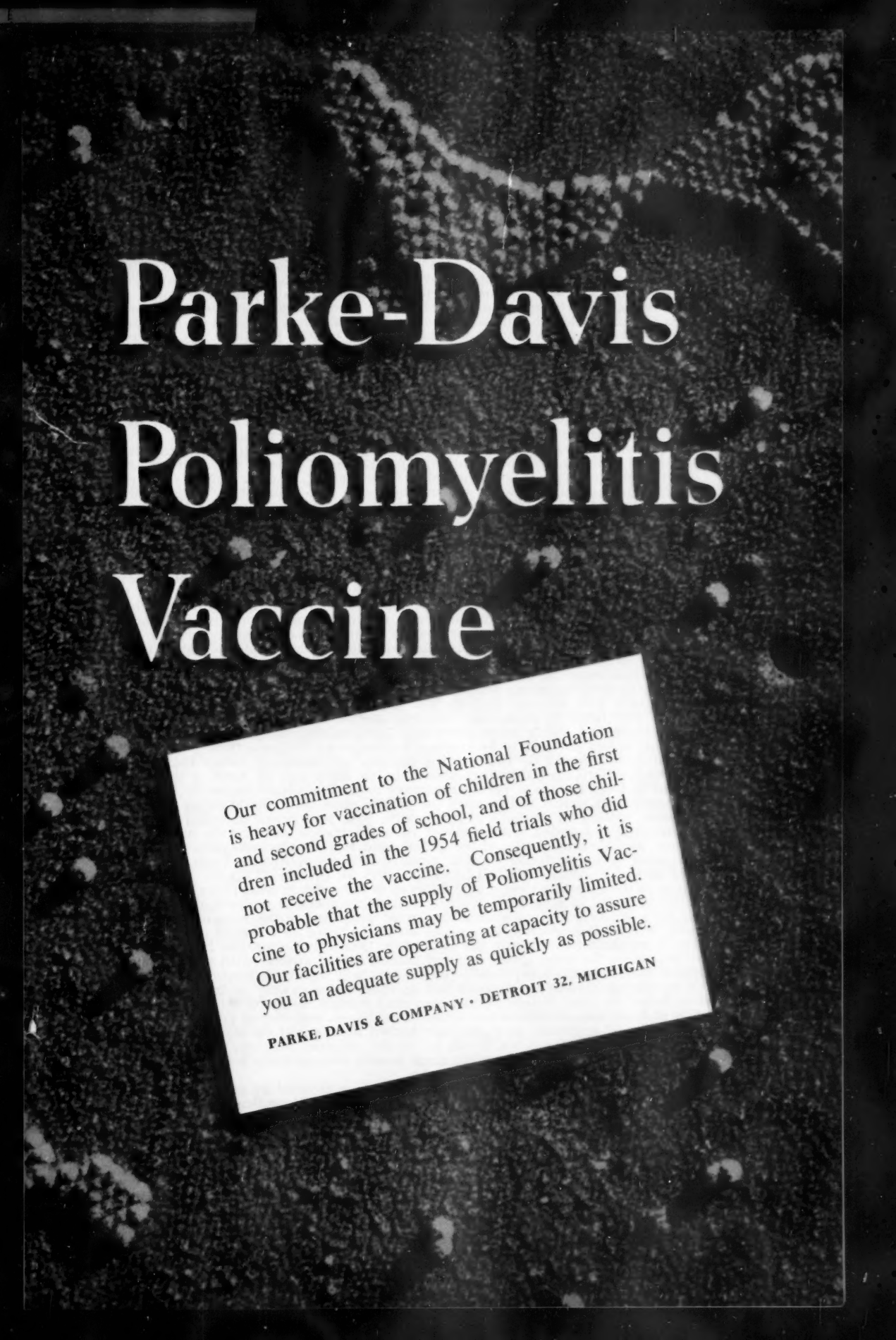
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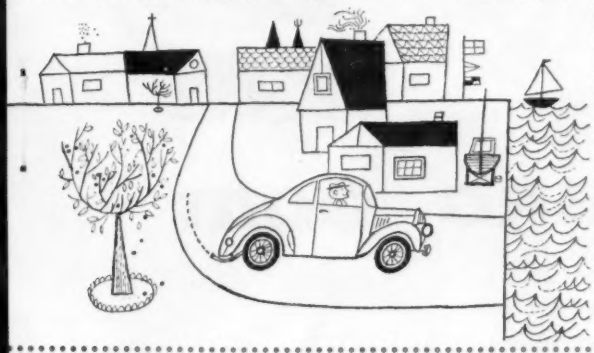

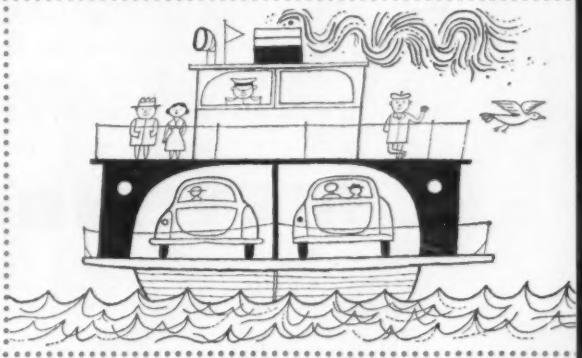

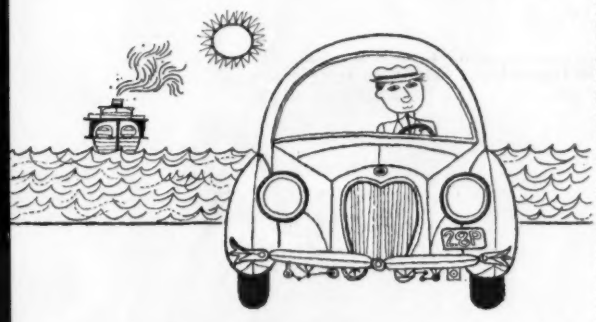

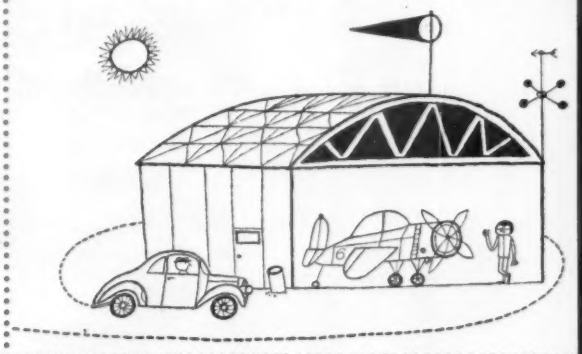

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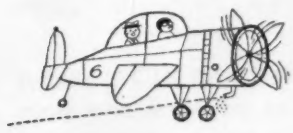

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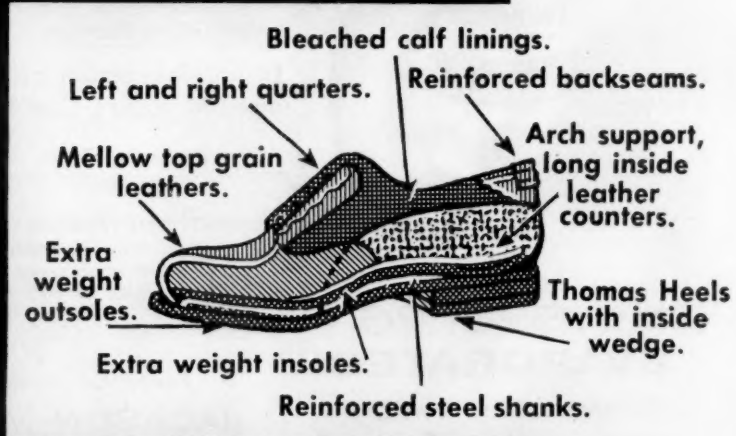

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Chlorpromazine in the Control of Vomiting in Children

Preliminary Clinical Evaluation

C. W. DAESCHNER, M.D.
JOHN L. CLARK, M.D.
G. Y. GEORGE, M.D.
and
R. A. FRANKEL, M.D., Houston, Texas

Vomiting is both a common and an important therapeutic problem in children. Every physician is aware of the extreme dehydration that may quickly follow its onset. A drug which appears to be a safe and effective agent for the control of vomiting is now available in the form of chlorpromazine hydrochloride * (10-[γ-dimethylaminopropyl]-2-chlorophenothiazine hydrochloride). Boyd and co-workers † and Cook and Toner [3] have shown that this drug inhibits apomorphine-induced emesis in animals. These studies suggest that chlorpromazine acts by depressing the vomiting center within the central nervous system, thus blocking the vomiting reflex.

Several forms of side-reaction have been described in connection with chlorpromazine therapy. A sedative effect of variable degree is seen in the majority of successfully treated patients. This effect is most pronounced after the first dose and usually disappears within a few hours. Pharmacological studies by Moyer and co-workers [4] reveal that in the usually administered therapeutic doses chlorpromazine does not significantly influence renal function or cardiac output. Chronic toxicity studies do not show evidence of depression of hemopoietic activity, however, leucopenia and agranulocytosis, though rare, have been reported in patients receiving chlorpromazine.‡ Although laboratory studies [4] have failed to demonstrate evidence of liver toxicity, occasional reports of jaundice in the course of chlorpromazine administration have appeared. Moyer § encountered 5 instances of jaundice in over 900 patients treated with chlorpromazine. The jaundice cleared when the drug was discontinued and left no demonstrable evidence of residual liver damage. A few instances of allergic skin reactions are described in the literature.[5]

Studies in adults ‖ support the statement that chlorpromazine is both a safe and a potent antiemetic agent, however, similar studies in children have not yet appeared in the American literature. The authors have undertaken a study to define effective dosage schedules for children, to evaluate therapeutic efficacy, and to observe side-effects of chlorpromazine therapy.

MATERIAL AND METHODS

During a period of 18 months, 100 clinical trials of chlorpromazine were carried out in 92 infants and children. The patients, ranging from 6 weeks to 14 years of age, manifested vomiting as a symptom associated with a variety of conditions (Table 1).

From the Department of Pediatrics, Baylor University College of Medicine, and the Pediatric Service, Jefferson Davis Hospital.

* Supplied by Mr. R. Michael Buckley, of Smith, Kline & French Laboratories, as Thorazine, S. K. F.

† References 1 and 2.

‡ Smith, Kline & French Laboratories: Personal communication to the authors.

§ Moyer, J. H.: Personal Communication to the authors.

‖ References 6-9.

TABLE 1.—*Summary of the Etiological Types of Vomiting and the Clinical Response to Therapy in One Hundred Cases*

Etiology of Vomiting	No. of Cases	Therapeutic Response			
		Excellent	Good	Equivocal	None
Acute nonspecific gastroenteritis	42	24	12	5	1
Gastroenteritis associated with acute infection	24	14	8	2	..
Functional vomiting	5	2	2	..	1
Chalasia of esophagus	2	..	2	..	..
Ketogenic diet	2	1	1	..	..
Diabetes mellitus with acidosis	4	2	1	1	..
Adrenogenital syndrome	2	1	1	..	..
Postirradiation therapy					
Acute leukemia	1	1	..	..	..
Lymphosarcoma	1	..	1	..	..
Sacrococcygeal malignancy	1	1	..	..	..
Nephroblastoma	1	..	..	1	..
HN_2 therapy (Hand-Schüller-Christian syndrome)	1	1	..	..	..
Acute chemical gastritis due to					
Acetylsalicylic acid therapy	1	..	1	..	..
Hydrocarbon	1	1	..	..	..
Pyloric stenosis	2	..	..	..	2
Skull fracture	1	1	..	..	..
Osteogenic sarcoma—terminal	1	1	..	..	..
Bulbar polio (postacute)	4	1	1	..	2
Laryngotracheobronchitis	2	..	1	..	1
Acute appendicitis	1	..	1	..	..
Encephalitis, measles	1	..	..	..	1
Total	100	51	32	9	8

The following procedure was used in evaluating patient response to chlorpromazine therapy. Only patients with a history of significant vomiting were included in the study. They were placed on a calculated dose of chlorpromazine, as outlined in Table 2. The child was offered a normal diet for age and was given antibiotic or chemotherapy as indicated. Parenteral fluids were given in only nine cases. If the patient took a normal quantity of food and fluid without further vomiting the result was considered "excellent." In patients in whom vomiting was controlled but intake was not normal or in children who vomited occasionally but who gained weight and remained hydrated, the response was described as "good." In some instances occasional vomiting continued or parenteral fluids were given prophylactically. These results were recorded as "equivocal." If vomiting continued without change or if hydration could be maintained only by use of parenteral fluids, the response to medication was recorded as "none." In most instances the initial dose of chlorpromazine was given intramuscularly or per rectum. Patients usually required only 12 to 24 hours of therapy; however, if more prolonged medication was necessary, syrup or tablet preparations of chlorpromazine were substituted as soon as the initial tendency to vomiting subsided. Usually oral medication was given at 4- to 6-hour intervals, but in a few instances satisfactory control was possible using a 12-hour dosage schedule. Several patients were treated at more than one dosage schedule in an effort to determine the most effective dose range. The intramuscular material was given as a solution in normal saline ranging in concentration from 1.0 to 5.0 mg. per cc. The syrup contained 2.5 mg. per cc. (10 mg/4 cc.), and the tablets were prepared to contain 5.0, 10.0, or 25.0 mg., depending on dose desired. The suppositories contained from 25-50 mg. (Where smaller per rectum doses were required these were sliced logitudinally.) A standardized check sheet record was maintained

TABLE 2.—*Individual Dosage Schedule for Chlorpromazine* Therapy in Children*

Dosage Form	No. of Cases	Dose, Mg./Kg.	Complaints
Intramuscular	52	0.5	No complaints when used in a concentration of 5 mg./cc. or less
Syrup (2.5 mg./cc.)	36	1.0	Well accepted and no aftertaste
Tablets (10 & 25 mg.)	14	1.0	.....
Suppository	31	2.0-3.0	No complaints †

* Several patients received more than one dosage form.
† See also Table 5 on proctoscopic studies.

on each patient receiving chlorpromazine therapy. Particular emphasis was placed upon the recording of any side-reactions.

RESULTS

Table 1 summarizes the therapeutic response in the various etiological groups. In 83 cases the response was considered excellent or good. These infants and children were restored to and maintained in a satisfactory state of hydration without resort to parenteral fluids. Nine additional patients were either incompletely controlled with chlorpromazine therapy or parenteral fluids were given prophylactically because of the serious degree of the patient's antecedent dehydration. Only eight patients in this series did not improve during chlorpromazine therapy. Table 3 lists the patient's response according to age of the patient. As might be expected, the majority of the patients treated for vomiting were under 5 years of age. Evaluation of therapeutic effect according to the sex of the patient revealed no significant difference between males and females.

TABLE 3.—*Distribution of Therapeutic Response According to Age of Patient*

Age, Yr.	No. of Cases	Therapeutic Response			
		Excellent	Good	Equivocal	None
1	39	17	12	5	5
2	16	10	5	1	..
3	9	5	3	0	1
4	8	3	2	3	0
5	5	2	2	0	1
6	5	3	1	0	1
7	1	1	0	0	..
8	4	2	2	..	..
9	0	..	..	..	..
10	2	2	..	..	..
11	4	2	2	..	..
12	2	2	..	..	..
13	4	1	3	..	..
14	1	1	..	..	..
Total	..	51	32	9	8

COMMENT

A number of problems are encountered in the evaluation of a new antiemetic medication such as chlorpromazine in the symptomatic treatment of vomiting. Acute vomiting is frequently self-limited; therefore, the first 40 patients in this series were hospitalized for treatment. They were given a single parenteral dose of chlorpromazine after emesis was observed. In some of these patients vomiting recurred 8-12 hours later, suggesting that the emetic factors were still present. In all instances only those patients with significant vomiting were included in the study. In addition, vomiting associated with acute infectious processes frequently decreases as specific therapy controls the infection. In this series all children were fed 45 minutes to an hour after the antiemetic medication was given and before significant antibiotic or chemotherapeutic effect could be expected. It is also well known that sedation decreases the tendency to emesis. The majority of our successfully treated patients showed some soporific effect; however, sedation did not persist as long as did the antiemetic effect, and in some patients a very transient sedative action was associated with an excellent antiemetic effect.

The patients in whom chlorpromazine therapy failed to control vomiting are of particular interest. Two of these were organic obstructions (pyloric stenosis) later relieved by operation. These two infants were moderately sedated and showed an increased interval between episodes of vomiting; however, the quantity of each emesis was unusually large and felt to represent accumulation of the interval feedings. Earlier in our clinical studies, an infant with chalasia of the esophagus and vomiting had temporarily been controlled with chlorpromazine. He was readmitted to the hospital some two months later with measles encephalitis (typical rash and spinal fluid pleocytosis) and a recurrence of vomiting which persisted in spite of the intramuscular administration of chlorpromazine. Chlorpromazine was given to an 11-month-old infant with an undiagnosed disease characterized by extreme chronic malnutrition and long-standing vomiting. He showed some improvement in his tendency to vomit while receiving therapy, but daily parenteral fluids were still necessary. Forty-two infants and children with

TABLE 4.—*Side-Effects Noted in the Course of Treating One Hundred Cases of Vomiting with Chlorpromazine*

Symptoms	No. of Cases
Lethargy	
None	16
Mild	52
Moderate	24
Severe	8
Fainting	1
Dizziness	2
Total	103

acute nonspecific gastroenteritis and vomiting were treated with chlorpromazine. Five of these patients were incompletely controlled, and occasional vomiting continued, or the use of parenteral fluids was necessary to maintain hydration. Only one patient in this group could be considered unimproved on chlorpromazine therapy. Two children in the postacute phase of bulbar poliomyelitis who were emotionally unstable and had intermittent periods of anorexia, nausea, and vomiting failed to respond to prolonged oral chlorpromazine therapy. These patients showed no soporific effect. Vomiting associated with severe paroxysms of coughing due to acute laryngotracheobronchitis was observed in two patients. Chlorpromazine therapy was associated with improvement in one child but failed to prevent emesis in the second case. Several patients who were vomiting in association with other upper respiratory infections responded well to chlorpromazine therapy.

Side-effects were largely limited to various degrees of depression of the sensorium (Table 4). Only 16 patients failed to demonstrate this manifestation. Sedation was most prominent following the first dose of chlorpromazine and was less noticeable following each successive dose. As shown in Table 4, the degree of lethargy in eight patients was classified as severe. These patients were difficult to arouse and seemed disoriented when finally awakened. They could, however, take oral fluids, and the sedative effect gradually disappeared in from three to eight hours. Deep sedation seemed more often associated with intramuscular type treatment and was least often seen when the medication was administered orally. Similarly, deep sedation was more often seen in the patients who were dehydrated and drowsy from their primary disease. It has been our impression that where larger doses are needed, a gradual increase in the dose seems to minimize the sedative effect.

Ten convalescent patients were given chlorpromazine by suppository in multiple doses over a three- five-day period. No patient complained of discomfort from this medication. At the end of this time careful proctoscopic examination failed to reveal any evidence of anorectal irritation (Table 5).

An attempt has been made to establish a dose-effect relationship for chlorpromazine

TABLE 5.—*Study to Determine Effects of Chlorpromazine in Suppository Form upon the Anorectal Mucous Membranes*

Patient	Weight, Kg.	Age	Diagnosis *	Dose Schedule	Proctoscopic Findings
L. C.	35	12 yr.	Rheumatic fever	12.5 mg. q. 6 h. × 17	Normal
N. Q.	30	8 yr.	Meningococcemia	12.5 mg. q. 6 h. × 13	Normal
R. M.	29	7 yr.	Rheumatic fever	12.5 mg. q. 6 h. × 17	Normal
G. B.	27	8 yr.	Hemophilia	12.5 mg. q. 6 h. × 21	Normal
A. J.	26	8 yr.	Rheumatic fever	12.5 mg. q. 6 h. × 21	Normal
G. H.	24	7 yr.	Hydronephrosis	25.0 mg. q. 8 h. × 11	Normal
G. C.	11	1 yr.	Lye burns of mouth	12.5 mg. q. 8 h. × 11	Normal
H. W.	8	9 mo.	Retropharyngeal abscess	12.5 mg. q. 8 h. × 11	Normal
J. W.	8	8 mo.	Bronchiolitis	17.5 mg. q. 8 h. × 11	Normal
J. A.	7	6 mo.	Foreign body in larynx	12.5 mg. q. 8 h. × 11	Normal

* All patients were convalescent at time of chlorpromazine study.

in children. Table 2 tabulates the dose range based on our clinical experience. In general the intramuscular route gives the most consistent response, although an equivalent dose per rectum may be equally effective. It is usually efficacious to begin with an appropriate intramuscular or rectal dose of chlorpromazine and continue this route of medication at four-hour intervals until the tendency to vomit is brought under control. The patient may then be maintained on oral syrup or tablet preparations of chlorpromazine given at four- to eight-hour intervals as long as antiemetic effect is desired.

The only specific contraindication to chlorpromazine therapy we have encountered thus far appears to be organic obstruction of the gastrointestinal tract. When vomiting is an important diagnostic or prognostic consideration (i. e., intestinal obstruction or head injuries), chlorpromazine should be used judiciously and with the full recognition that it produces only symptomatic control of vomiting. Though not a contraindication to chlorpromazine therapy, the need for emergency restoration of fluid balance or homeostasis in critically dehydrated children usually precludes sole reliance on the oral route for rehydration.

SUMMARY AND CONCLUSIONS

A preliminary clinical trial of chlorpromazine (Thorazine, S. K. F. [10-(γ-dimethylaminopropyl)-2-chlorophenothiazine hydrochloride]) as an antiemetic agent in children suggests that it is both safe and effective.

One hundred clinical trials have been carried out in 92 infants and children vomiting from a wide variety of causes. In 83 of these patients the response was graded as excellent or good. In an additional nine there was a decrease in the vomiting, but the role of chlorpromazine was not definite. In eight patients no clinical improvement was noted.

Although toxicity has not been a significant factor in the present authors' experience, and reports of toxicity in the literature are rare, chlorpromazine is a new drug, and certain precautions in its use should be exercised:

1. In patients receiving therapy for more than a few days the possibility of agranulocytosis should be considered.

2. It would seem injudicious to treat patients known to have liver disease or jaundice with chlorpromazine, and certainly the drug should be discontinued in any patient in whom jaundice appears.

3. A mild and sometimes very helpful soporific effect is a common companion of effective chlorpromazine therapy. Pharmacologic studies have shown that when chlorpromazine is given concomitantly with central-nervous-system-depressant drugs it may potentiate their effect.

4. The cause of vomiting should be determined prior to therapy with chlorpromazine, since the latter may mask valuable diagnostic or prognostic signs and symptoms. Its use as an antiemetic in central-nervous-system injury or intestinal obstruction is debatable.

The effective dose of chlorpromazine varies with the route of medication. A dose of 0.5 mg. per kilogram is usually effective for intramuscular therapy, while oral therapy requires 1.0 mg. per kilogram for equivalent response. The tablet and syrup preparations appear equally effective as oral medicaments. When chlorpromazine is given by suppository, a dose of from 2-3 mg. per kilogram is necessary to obtain satisfactory therapeutic results. All dosage forms were well received and produced no evidence of local irritation and no unusual discomfort to the patient.

Chlorpromazine is an effective antiemetic agent for the symptomatic control of vomiting in children. It appears to have a wide range of usefulness.

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The Intestinal Flora in the Etiology of Infantile Infectious Diarrhea

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During the years 1949-1952, infectious diarrhea in infancy became a major health problem in Israel. Immigration reached such dimensions that the majority of immigrants had to be housed in tents or canvas huts concentrated in large camps. The overcrowding reached dangerous dimensions, sanitation was very primitive, and the average standard of hygiene of the immigrant population was low. Most of the people came from countries with a high infant mortality rate, and the families were quite used to the sight of sick infants dying. In contrast to this was the older established population (which did not number more than the immigrants), with a comparatively high standard of living and a very low infant mortality rate. Here infectious diarrhea was sporadic or limited to institutional outbreaks. With the beginning of mass immigration in 1949, the children's wards in the hospitals were flooded with cases of infectious diarrhea in all stages of dehydration. Practically all the cases came from immigrant centers, and the older established population was almost untouched by this epidemic.

We decided to use the opportunity to investigate the intestinal floras of infants ill with acute diarrhea and to compare them with the floras of healthy babies living in different socioeconomic conditions.

This study was aided by a grant from the Research Council of Israel.

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MATERIAL

The material investigated consisted of stool specimens obtained from infants up to the age of one year. All sick infants were admitted to a special ward of the children's department. Every third case was arbitrarily chosen for the investigation, but cases with positive cultures of Shigella or Samonella were not included. One hundred sixteen sick infants were finally investigated. The first stool spceimen was taken immediately after admission, before any treatment was started. All infants investigated received the same treatment and were under the same regimen. In 30 cases, 4 stools were examined, and in the remainder, from 3 to 10 stools. The first stools of the 116 sick infants are hereafter termed "clinical material."

As control, three groups of healthy infants were used. The first consisted of 85 babies living in camps, the second, of 155 babies from the harbor district of Haifa, and the third of 97 babies living in clean and properly kept communal nurseries. In all, 337 healthy infants were examined. In 30 infants, three stool specimens were examined, and in the remainder, one specimen only. The first stools of these healthy infants are termed "control material."

METHODS

Fecal specimens or rectal swabs were plated on SS agar and bromothymol blue lactose agar and cultivated for 18 hours in enrichment tetrathionate broth of Müller Kauffmann, from which subcultures were made on SS agar and bromothymol blue lactose agar.

For counting red colonies on SS agar and bromothymol blue lactose agar a fecal specimen of 1 gm. weight was suspended in 10 ml. normal saline and 0.5 ml. was stroked on the plate; 100 colonies were counted.

From each plate, 6 to 15 colonies were isolated which showed differences in color, dimension, or transparency. From the same specimen a minimum of 20 to 30 colonies were typed. Each colony was inoculated on triple-sugar iron agar and urea

lactose medium (Singer [7]) and from triple-sugar agar on Christensen urea medium and semisolid agar, 0.25%, and agar slant. All strains were identified after the primary differentiation according to their biochemical and serological properties. Enterococci, staphylococci, and Gram-positive anaerobes were not studied. The nomenclature adopted for the classification of Enterobacteriaceae was that of the Report to the International Congress of Microbiology in Rio de Janeiro, in 1950, as described by Kauffmann [5] and Kauffmann and Edwards [6] and for the classification of paracolon bacilli according to the scheme suggested by Borman and co-workers,[2] incorporated in "Bergey's Manual of Determinative Bacteriology," 1948.[1]

The criteria adopted for the inclusion of strains in the groups or subgroups were as follows.

Escherichia.—Rapid fermentation of lactose, IMViC reactions, nondecomposition of urea, and no liquefaction of gelatin. Composite growth obtained by needle strokes across the plates or single E. coli strains from triple sugar iron agar were tested by slide agglutination with Bacterium coli O111: B_4, O55: B_5, and O26: B_6 antiserum.

Paracolobactrum Coliforme.—The same method used for identification of Escherichia with the difference of late or no fermentation at all of lactose.

Klebsiella.—Rapid fermentation of lactose, IMViC reactions, decomposition of urea and biochemical behavior on adonitol, inositol, utilization of *d*-tartrate, sodium citrate and mucate and liquefaction of gelatin. Strains with the same properties as Klebsiella but which liquefied gelatin and according to Brooke [8] belong to B. colacae were included in the Klebsiella group.

Paracolobactrum Aerogenoides.—The same biochemical properties of Klebsiella group, many strains not capsulated, late or no fermentation at all of lactose, many Voges-Proskauer and methyl red positive reactions.

Bethesda, Providence, Proteus Rettgeri Strains.—According to their biochemical properties described in previous papers, Singer,[8] Singer and Bar-Chay.[9]

Proteus Vulgaris, Mirabilis, Morganii.—Decomposition of urea, swarming phenomenon on agar plate at room temperature, indole and H_2S production, fermentation of mannitol, maltose, sucrose with or without production of gas and liquefaction of gelatin.

Pseudomonas.—The ability to form pigment at 37 C, hemolytic action on sheep blood agar, acid production in xylose, and pellicle formation in peptone water media. No species differentiation was made.

Alcaligenes.—Strains which do not produce acid or gas from carbohydrates, do not form acetylmethylcarbinol, and are indole negative.

More than six O (boiled) and six H (formalinized) suspensions and corresponding antisera in rabbits according to Kauffmann's [5] method were prepared from every representative biochemical type of Bethesda, Providence, P. rettgeri, P. morganii, P. aerogenoides, and P. coliforme.

Representative biochemical strains of Klebsiella species were sent to Dr. Ida Ørskow, Statens Serum Institute, Copenhagen, for capsular type determination; Bethesda and Providence strains to Dr. R. P. Edwards and Dr. H. W. Ewing, Communicable Disease Center, Atlanta, Ga., and some Paracolobactrum strains to Dr. C. A. Stuart and M. Greenstein, Brown University, Providence, R. I., for serological identification.

TABLE 1.—*Number of Colonies of Lactose-Fermenting Organisms on SS Agar and Bromothymol Blue Lactose Agar*

	Clinical Material		Control Material	
No. Colonies	Stools	Per Cent	Stools	Per Cent
100-90	49	42.2	251	74.2
89-80	8	6.8	13	3.8
79-70	2	1.7	8	2.3
69-60	2	1.7	8	2.3
59-50	10	8.6	10	2.9
49-40	12	10.3	19	5.6
39-30	5	4.3	7	2.1
29-20	8	6.8	3	0.9
19-10	4	3.4	3	0.9
9- 0	16	13.8	15	4.4

From the same specimen different biochemical and serological type strains within the same group of bacteria were identified. All the strains with common biochemical behavior and serologically related were included in the groups or subgroups as described. The serological properties of the strains included in this paper, hemagglutination properties, antibody response in serum of children, and antibiotic spectrum, will be reported elsewhere.

RESULTS

In the first stage of this investigation a gross division of the material was made, according to the number of colonies of lactose-fermenting organisms counted per 100 colonies on SS agar and bromothymol blue lactose agar (Table 1).

The incidence of pure cultures of lactose-fermenting organisms in the clinical material was 42.2% in comparison with an incidence of 74.2% in the control material.

TABLE 2.—*Frequency of Isolation of Lactose-Fermenting Organisms in Three Different Groups of Controls*

		No. Cases	No. Isolations	Per Cent
Clinical material		116	49	42.2
Control material	Group I	85	52	61.1
	Group II	155	113	72.9
	Group III	97	86	88.6

The incidence of pure culture of late and nonfermenting organisms was 13.8% in the clinical material and 4.4% in the control material.

The controls consisted of three groups of healthy infants as previously described. Table 2 shows the difference in the frequency of isolation of lactose-fermenting organisms in these three groups of infants.

The inference to be drawn from Table 2 is that the better the living conditions of a group of infants, the higher the incidence of pure cultures of lactose-fermenting bacilli and vice versa. In localities with poor sanitary conditions the incidence of pure culture of lactose-fermenting bacilli was almost as low as in the group of infants ill with diarrhea.

An alternative classification of the results compares the number of bacterial groups isolated from infants ill with diarrhea with those of healthy infants (Table 3).

The average number of bacterial groups isolated from the clinical material was 3.69 per stool specimen, but up to 9 bacterial groups per stool were isolated. In the control material not more than six bacterial groups per specimen were isolated, and the average was 2.57.

TABLE 3.—*Number of Bacterial Groups per Stool Specimen*

No. Bacterial Groups	Clinical Material		Control Material	
	Cases	Per Cent	Cases	Per Cent
1	7	6	34	10
2	24	20.6	132	39.1
3	38	32.7	124	39.1
4	16	13.7	38	11.2
5	9	7.7	7	2
6	10	8.6	2	0.59
7	6	5.1	..	....
8	5	4.3	..	....
9	1	0.86	..	....
Total	116	....	337	....

All organisms were isolated on direct plating and on Müller Kauffmann's enrichment medium. In comparing the results obtained by the two methods, there are certain differences (Table 4).

The figures shown in the column "enrichment" are the number of bacterial groups in addition to those obtained by direct plating. The number of bacterial groups isolated from the clinical material on direct plating is, on the average, higher by one bacterial group than in the control material. The number of additional bacterial groups obtained by enrichment only is the same for the clinical group and the control groups.

On comparing the results of the two parts of Table 5, certain differences are apparent. Providence, P. rettgeri, P. morganii, Alcaligenes, and Pseudomonas are seen more frequently on direct plating of the clinical material than on the controls. The frequency of isolation of the same bacterial groups on enrichment medium of Müller Kauffmann is higher in the control material than in the clinical cases. Escherichia and P. coliforme were generally inhibited by the enrichment medium.

TABLE 4.—*Number of Bacterial Groups per Stool Specimen*

	Direct Plating	Enrichment	Total
Clinical material	2.85	0.84	3.69
Control material	1.68	0.89	2.57

On dividing the isolated bacterial groups according to their incidence in both the clinical and the control material, a certain pattern becomes apparent (Table 6).

The bacterial groups which were constantly found in similar number in both investigated groups of cases seem to constitute the resident flora of the intestinal tract. They are Escherichia, Klebsiella, P. coliforme and P. aerogenoides. The two latter bacterial groups appear to belong to the Escherichia and Klebsiella groups but behaved differently from them during the course of this investigation. The other bacterial groups were found in comparatively small number,

TABLE 5.—*Frequency of Isolation of Intestinal Bacteria on Direct Plating and on Enrichment Medium*

Bacterial Groups and Subgroups	Clinical Material				Control Material			
	Direct		Enrichment		Direct		Enrichment	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Escherichia	96	82.7	2	1.7	299	88.7	3	0.89
P. coliforme	27	23.2	1	0.8	46	16.3	7	2.07
Klebsiella	49	42.2	18	15.5	85	25.2	70	20.7
P. aerogenoides	15	12.9	13	11.2	25	7.4	13	3.8
Bethesda	3	2.5	1	0.8	1	0.2	..	....
Providence	10	8.6	2	1.7	8	2.3	..	....
P. rettgeri	10	8.6	2	1.7	..	....	3	0.8
P. morganii	35	30.1	15	12.9	31	9.1	31	9.1
P. mirabilis	43	37.0	31	26.7	65	19.2	125	37.0
P. vulgaris	1	0.8	..	....	3	0.8	7	2.0
Alcaligenes	18	15.5	4	3.4	5	1.4	10	2.9
Pseudomonas	14	12.0	9	7.7	2	0.5	30	8.9

and their incidence differed in accordance with the material. These seem to constitute the transient flora and consist of the groups Bethesda, Providence, P. rettgeri, P. morganii, P. vulgaris, Alcaligenes, and Pseudomonas. The cases of diarrhea were characterized by a general increase of these transient bacterial groups.

The Residential Bacterial Groups.—Escherichia was isolated in 84.5% of the clinical and in 89.5% of the control material. Serotype O111 : B_4 was found in 3.45% out of the clinical to 2.08% of the control material. The comparative figures for serotype O55 : B_5 were 1.72% to 1.48%, respectively. In the controls all determinations were made in the same nursery at a time when there were no cases of diarrhea.

P. coliforme was isolated in 24.1% of the clinical and in 15.7% of the control material. On direct plating, the figures were 23.27% and 13.64%, respectively. The increase in the frequency after enrichment was 0.86% and 2.07%, and thus these organisms follow the same pattern as Escherichia. In spite of this, there is an increase in the incidence of this organism in diarrhea.

Klebsiella was isolated in 57.7% of the clinical and in 46% of the control material. They were found on direct plating in 42.3% and in 25.21%, respectively.

P. aerogenoides was isolated in 24.1% of the clinical and in 11.3% of the control material. The figures on direct plating were 12.93% and 7.41%, respectively. This organism is related to the Klebsiella group, but there seem to be certain strains of Paracolobactrum, the incidence of which is so increased in cases of diarrhea that it arouses suspicion of their role in the etiology of diarrhea.

P. mirabilis was isolated in 63.8% of the clinical and in 56.4% of the control material. On direct plating the respective figures were 37.06% and 19.28%. There is an increased incidence on direct plating of the clinical material.

The Transient Group of Intestinal Bacteria.—With the exception of P. mirabilis, which is considered here as belonging to the resident intestinal flora, the other subgroups of Proteus, including Providence, constitute the largest contingent of the transient flora.

P. morganii was found in healthy babies, but its incidence rose with the lowering of

TABLE 6.—*Frequency of Isolation of Intestinal Bacteria in the Clinical and in the Control Material*

Bacterial Groups and Subgroups	Clinical Material		Control Material	
	Cases	Per Cent	Cases	Per Cent
Escherichia	98	84.5	302	89.5
P. coliforme	28	24.1	53	15.7
Klebsiella	67	57.7	155	46.0
P. aerogenoides	28	24.1	38	11.3
Bethesda	4	3.5	1	0.3
Providence	12	10.3	8	2.4
P. rettgeri	12	10.3	3	0.9
P. morganii	50	43.1	62	18.4
P. mirabilis	74	63.8	190	56.4
P. vulgaris	1	0.9	10	3.0
Alcaligenes	22	19.0	15	4.5
Pseudomonas	23	19.8	32	9.5

TABLE 7.—*Frequency of Isolation of Intestinal Bacteria in Four Consecutive Examinations*

Bacterial Groups and Subgroups	Clinical Material								Control Material							
	1st Examination		2d Examination		3d Examination		4th Examination		1st Examination		2d Examination		3d Examination		4th Examination	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Escherichia	25	83.3	25	83.3	25	83.3	25	83.3	29	96.6	26	86.6	21	69.9	21	69.9
P. coliforme	8	26.6	6	19.9	7	23.3	4	13.3	5	16.6	5	16.6	2	6.6	2	6.6
Klebsiella	20	66.6	19	63.3	19	63.3	18	59.9	20	66.6	22	73.3	25	83.3	22	73.3
P. aerogenoides	9	27.9	5	15.6	5	15.6	8	26.6	6	19.9	6	19.9	5	16.6	10	33.3
Bethesda	..	....	..	....	..	....	..	....	..	....	1	3.3	..	....	..	....
Providence	4	13.3	5	15.6	3	9.9	2	6.6	3	9.9	3	9.9	2	6.6	3	9.9
P. rettgeri	3	9.9	2	6.6	3	9.9	1	3.3	..	....	..	....	..	....	..	....
P. morganii	10	33.3	12	39.9	7	23.3	9	27.9	11	36.6	10	33.3	12	39.9	7	23.3
P. mirabilis	18	26.6	20	66.6	23	76.6	23	76.6	11	36.6	16	53.3	17	56.6	22	73.3
P. vulgaris	..	....	..	....	..	....	1	3.3	..	....	..	....	..	....	..	....
Alcaligenes	5	15.6	4	13.3	4	13.3	4	13.3	..	....	..	....	1	3.3	..	....
Pseudomonas	4	13.3	4	13.3	5	16.6	8	26.6	5	16.6	4	13.3	2	6.6	1	3.3

TABLE 8.—*Frequency of Isolation of Intestinal Bacteria in Mild and Severe Diarrhea*

Bacterial Group and Subgroups	Mild Diarrhea		Severe Diarrhea	
	Cases	Per Cent	Cases	Per Cent
Escherichia	19	95	20	100
P. coliforme	6	30	7	35
Klebsiella	16	80	14	70
P. aerogenoides	9	45	4	20
Bethesda	3	15	1	5
Providence	6	30	6	30
P. rettgeri	4	20	4	20
P. morganii	10	50	14	70
P. mirabilis	14	70	19	95
P. vulgaris	..	..	..	..
Alcaligenes	12	60	6	30
Pseudomonas	8	40	7	35

hygiene standards. However, all groups of healthy infants show an equal frequency of isolation on direct plating and on enrichment, whereas the diarrhea groups show a predominance of isolation on direct plating.

P. vulgaris was isolated in four cases, all of them from one single nursery and in one case of diarrhea only.

P. rettgeri was isolated in 10.3% of the clinical material. Its incidence in healthy babies was 0.89% only, and all cases were from one single nursery.

Providence, which may be related to the Proteus, has been isolated in 10.3% of the clinical material as against 2.4% in the controls.

Bethesda was found four times in the clinical and once in the control material.

A. faecalis was isolated in 1.9% in the clinical material as against 4.5% in the control material. Its incidence on direct plating was 15.51% in the former and 1.48% only in the latter material.

Pseudomonas was isolated in 19.8% of the clinical as against 9.5% of the control material. Its incidence on direct plating was 12.06% in the former and 0.89% only in the latter material.

BACTERIOLOGICAL FOLLOW-UP

Thirty unselected cases of nonspecific infectious diarrhea were investigated four times each in the course of the illness (Table 7).

In each case there was no change in the incidence and frequency of the resident and transient bacterial strains during the course of the diarrhea until the patient recovered. Many of the transient bacteria persisted for a long time in the intestines of the healthy infants. It is concluded, therefore, that the transient flora may persist over a relatively long period of time, even when the metabolic conditions in the intestines have apparently returned to normal.

From the 116 cases of diarrhea the 20 mildest and the same number from among the severest cases were selected for comparison. The results are shown in Table 8.

It is seen that there is no correlation between the severity of a case of diarrhea and the bacterial picture as shown by the polymorphism of the intestinal flora and the frequency of isolation of the different bacterial groups. To compare the results of our investigation with the intestinal flora found in cases of specific diarrhea, 20 additional cases of diarrhea due to Shigella and 20 cases due to Salmonella were investigated. The results are shown in Table 9.

The pattern of the intestinal flora in the two additional groups of specific diarrhea is the same as in the 116 cases of nonspecific diarrhea. There is the same polymorphism of the intestinal flora and the same frequency of isolation of the different bacterial groups.

COMMENT

The investigation raises the question as to whether there is a relation between the epidemics of infectious infantile diarrhea on one

TABLE 9.—*Frequency of Isolation of Intestinal Bacteria in Twenty Cases of Shigella and Twenty Cases of Salmonella Infection*

Bacterial Group and Subgroups	Shigella		Salmonella	
	Cases	Per Cent	Cases	Per Cent
Escherichia	20	100	20	100
P. coliforme	7	35	6	30
Klebsiella	7	35	7	35
P. aerogenoides	6	30	6	30
Bethesda	1	5	1	5
Providence	4	20	2	10
P. rettgeri	1	5	2	10
P. morganii	9	45	9	45
P. mirabilis	12	60	11	55
P. vulgaris	..	..	..	..
Alcaligenes	3	15	1	5
Pseudomonas	2	10	1	5

hand and the polymorphism and shift to the transient groups of intestinal bacteria on the other. An answer to this question is possible only if we consider the intestinal flora as a whole and the changes of the bacterial population in the intestines in relation to the host and his metabolism. The babies investigated after their long exhausting journeys from their countries of origin were often in marked stages of clinical malnutrition. Their general resistance to infections was low. While the water supply in the immigrant camps was adequate, the supply of food, especially milk, was often insufficient and was always below accepted hygienic standards. Massive infection of food was always possible. On the other hand, the primitive sanitation of the camps and the personal habits of the majority of the immigrants made the camps ideal breeding grounds for all the intestinal bacteria. Large numbers of flies added to the possibilities of infection. Under these conditions, massive infections with bacteria of infants in a state of disordered metabolism were possible, whereas under ordinary conditions these bacteria do not have the opportunity to invade the intestines. The transient bacteria found during this investigation in the sick infants and in the apparently healthy infants from the camps had ample opportunities to infect these children. The addition of a transient strain to the resident flora causes a disturbance of the bacterial equilibrium normally existing in the intestines. This alone may cause metabolic changes in the intestine which could be responsible for at least part of the diarrhea. In addition the disturbed balance of the intestinal flora by the invasion of one transient strain opens the way for secondary invasions by other strains and groups of bacteria. Finally, strains which were present previously in small numbers in the intestines have the opportunity to multiply and can be isolated by routine methods such as direct plating. Ultimately polymorphism of the flora develops, as was shown in this investigation. The enhanced communicability and invasiveness of these strains raises the question as to whether there is an increase in their virulence. One cannot answer this question, but it may be assumed that the conditions causing greater communicability and invasiveness possibly enhance the toxicity of the bacterial strain and simultaneously its virulence.

SUMMARY

The intestinal flora of 116 infants suffering from diarrhea and of 337 healthy infants was investigated. The clinical cases were admitted from overcrowded immigrant camps. The controls consisted of three groups of infants living in different conditions of hygiene and sanitation. No cases of Shigella or Salmonella infections were included. No evidence was found to incriminate one single potential pathogenic organism or a combination of more as the causative agent of infectious diarrhea. The incidence of late- and non-lactose-fermenting bacilli was definitely higher in the groups with diarrhea than in the control groups. In the groups of healthy infants the incidence of late- and non-lactose-fermenting bacilli rose as the general and hygienic conditions in which the infants were living became worse. There was a definite shift of the intestinal flora from lactose-fermenting organisms to late fermenters or nonfermenters.

The number of bacterial groups isolated per examination was greater in the diarrhea group than in the healthy babies. The same difference was seen in the single groups of the healthy babies. The additional organisms belonged to the late- or non-lactose-fermenting groups.

The bacteriological groups Escherichia, Klebsiella, P. mirabilis, P. coliforme, and P. aerogenoides were constantly found in equal numbers in both the clinical and the control material. They seem to constitute the resident flora of the intestinal tract. The groups Bethesda, Providence, P. rettgeri, P. vulgaris, P. morganii, Alcaligenes, and Pseudomonas were found in healthy infants occasionally and mostly after enrichment. In the clinical material they were often isolated on direct plating. They are the transient flora of the intestinal tract.

The cases of diarrhea were characterized by a general increase of these transient bacterial groups.

There was no change in the number of bacterial groups or in the incidence of the different strains during the course of diarrhea. The transient flora often persisted over a relatively long period of time after recovery of the patient.

No difference in the bacterial picture of cases of mild or severe diarrhea was seen. The same pattern of the intestinal flora was found in the additional cases of diarrhea with positive cultures of Shigella or Salmonella.

The possible explanation of the role of the transient bacteria in the etiology of infectious infantile diarrhea is given.

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Congestive Failure in the Newborn Caused by Cerebral A-V Fistula

A Clinical and Pathological Report of Two Cases

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Congestive failure with gross cardiomegaly is a relatively rare condition in the early neonatal period. From the etiological viewpoint, four main groups have to be considered. First, there are the developmental anomalies of the heart, chiefly aortic atresia, transposition of the great vessels, and true truncus arteriosus.[1] Secondly, there is the primary myocardial disease group,[2] which includes five pathological entities often indistinguishable clinically from each other. Thirdly, prolonged episodes of paroxysmal auricular tachycardia [3] may result in a very large heart. Lastly, extracardiac causes of increased cardiac output may also produce marked cardiac enlargement. The last group consists principally of two entities—a large patent ductus arteriosus [4] and severe hemolytic anemia, particularly erythroblastosis fetalis.[5] Potter [6] has added a third condition to this group, namely, multiple telangiectasias of the cerebral vessels. Still another, hitherto undescribed, extracardiac cause of marked cardiomegaly with congestive failure in a newborn infant has been encountered recently in two autopsied cases in this hospital. This entity consists of a large cerebral arteriovenous fistula resulting in gross cardiomegaly and death in the newborn period. This paper will present the clinical and autopsy findings in the two cases and will discuss briefly the physiological pathology responsible for the cardiac involvement.

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REPORT OF CASES

CASE 1.—Baby G., a boy, was referred to the Children's Medical Center at the age of 4 hours with a diagnosis of possible erythroblastosis fetalis. The child was the product of a pregnancy of a quintipara and sextigravida Rh-negative mother, whose other children were normal. The mother's membranes had ruptured two and one-half days prior to delivery, and she had an effective labor of 20 hours. The baby was cyanotic and apneic for a short period at birth, but responded well to resuscitation. He was placed in oxygen, where he remained dyspneic without cyanosis. A blood smear showed a preponderance of nucleated red blood cells.

Physical examination on admission to the Children's Medical Center revealed a cyanotic tachypneic baby. There was a thrill palpable in the right anterior neck. There was a loud systolic murmur over the entire precordium, loudest just to the right of the sternum. Cardiac rhythm was regular at a rate of 148. The edge of the liver was barely palpable. There was a soft 3 by 4 cm. tumor mass beneath the skin of the right frontal area.

Laboratory Studies.—RBC 3,800,000; Hgb. 17 gm. per 100 cc.; WBC 13,500, with normal differential except for 23 normoblasts per 100 WBC; 304,000 platelets; 12.6% reticulocytes. Blood type AB; Rh Positive. Coombs test negative.

Electrocardiogram.—Mild right ventricular hypertrophy, not abnormal for the age. ST and T wave changes suggesting myocardial damage.

Fluoroscopy.—Very large heart with poor expansion of the left lung.

Course.—The child was placed in an Isolette incubator and was offered nothing by mouth. After

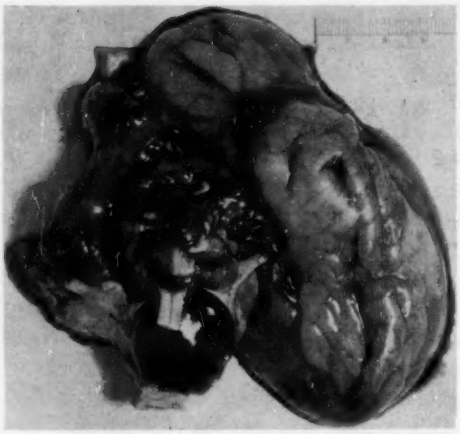
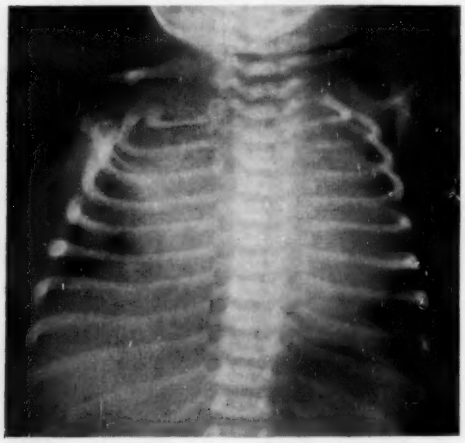


Fig. 1.—Photograph of brain in Case 1. Posterior superior view. Note the displacement of the left cerebral hemisphere by the large vascular mass.

12 hours his liver became palpable 2 cm. below the right costal margin. It was felt that the child was in congestive failure. Digitalization was begun, but he died before the digitalizing dose could be completed.

The pertinent findings at autopsy revealed a massive vascular network which almost entirely replaced the right cerebral hemisphere. This penetrated the right frontal bone and scalp to appear as several small hemangiomas on the skin of the right frontal area (Fig. 1). The left cerebral hemisphere was thin and flabby. The greatly dilated lateral ventricle was filled with clotted blood. Gross communications were demonstrated between branches of the right middle and posterior cerebral arteries and the greatly dilated superior sagittal sinus, making up an extensive arteriovenous fistula. Microscopically, there

Fig. 2.—Radiogram of heart in Case 2. Anteroposterior view. Note gross cardiomegaly.



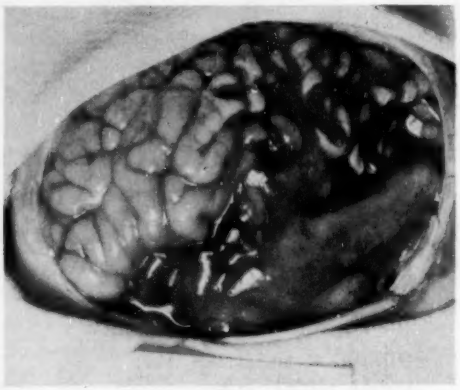


Fig. 3.—Left lateral view of brain in Case 2. Note the vascular mass displacing the left temporal and occipital lobes.

were abundant vascular channels replacing cerebral tissue. Some of these vessels were veins, some proved to be arteries, and others endothelium-lined sinusoids. The heart was greatly enlarged, weighing 36.5 gm. against an expected weight of 17 gm. It compressed the left lung. There was a patent foramen ovale measuring 1.2 by 0.6 cm. The left carotid artery arose from the innominate artery. The lungs microscopically showed atelectasis, edema, hemorrhage, focal bronchopneumonia, and congestion. The bone marrow showed erythroid hyperplasia. Postmortem blood and lung cultures were negative.

Case 2.—H. S., a baby boy, was referred to the Children's Medical Center at the age of 3 days. He was the product of the uncomplicated first pregnancy of a healthy mother. Labor lasted five to six hours. The baby was apneic at birth for a five-minute period, but responded to resuscitation. At 30

Fig. 4.—Cross section through left cerebral hemisphere of brain in Case 2.

hours, his respirations became grunting and rapid. Cyanosis and a heart murmur were noted then for the first time. At 3 days of age, hepatomegaly and cardiomegaly were noted. Digitalization was begun, and the child was transferred to the Children's Medical Center.

Physical examination on admission revealed an acutely ill child with respirations of 64 and pulse rate of 146. The cry was weak and shrill. The skin was mottled and cyanotic. A few inspiratory rales were heard at both lung bases. The heart was greatly enlarged. A Grade 3 systolic murmur was heard along the left sternal border. The liver was felt 6 cm. below the right costal margin. Neck veins were dilated.

Laboratory Studies.—Hgb. 17 gm. per 100 cc.; WBC 10,300.

Electrocardiogram.—Suggestion of right ventricular hypertrophy not abnormal at this age. Auricular hypertrophy.

Chest Film (Referring Hospital).—Gross cardiomegaly (Fig. 2).

Course.—The child was placed in an Isolette with oxygen and given prophylactic pencillin and streptomycin. A single dose of meralluride (Mercuhydrin), 0.1 cc., was administered intramuscularly. He died six hours after admission.

Autopsy Findings.—Over the left cerebral hemisphere, in the parietooccipital area, a large cirsoid aneurysm measuring in its entirety 4 by 4 cm. formed an arteriovenous fistula between the middle cerebral artery and the sigmoid sinus (Fig. 3). The lesion was made up of large tortuous channels, measuring up to 1.5 cm. in diameter. On dissection, it was seen that a single reversing loop of blood vessel accompanied by smaller varicose dilatations was taking origin from the middle cerebral and posterior communicating arteries around the aneurysm. The underlying gyral pattern of the brain was atrophied and distorted (Fig. 4). Microscopically, the vessels were large and thin-walled and appeared as arteries, veins, or intermediate structures (Fig. 5). The heart was large, weighing 39 gm. as compared with an expected weight of 17 gm. The foramen ovale was patent. The lungs showed some aspiration pneumonia and edema. Evidences of congestive cardiac failure were also seen in the liver, intestines, and pleural spaces.

COMMENT

The generally recognized clinical picture of congenital cerebral arteriovenous fistula, as described by Hamby,[7] is that of a lesion manifesting itself in adolescence or early adulthood by signs of increased intracranial pressure, by focal neurological signs, and by convulsive seizures. It represents about 0.5% to 1.0% of all intrancranial tumors in adults. According to Ingraham and Matson,[8] these lesions only occasionally become symptomatic in early childhood. A review of the literature reveals only an occasional instance where such a condition caused clinical difficulties in infancy.* No report of a case causing symptoms in the newborn period was found during a careful perusal of the literature.

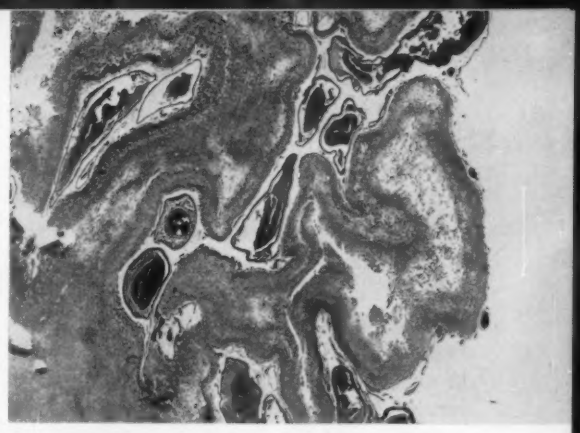


Fig. 5.—Microscopic section through part of lesion and adjacent cerebral tissue in Case 2; reduced approximately ½ from mag. × 24.

Cushing and Bailey[12] suggest that, although these lesions are usually dormant throughout infancy and childhood, they are probably present at birth. Then, during the adolescent or young adult age and occasionally as late as midadult life, some unknown stimulus sets the growth of the individual lesion in motion. It then becomes symptomatic in a manner varying with its location, size, and rate of growth.

The pathological picture, as described in the literature, does not vary significantly from the lesions in our two cases. Hamby[7] points out that there are two major types: (*a*) those with direct end-to-end connection between the artery and vein, and (*b*) those with a network of undifferentiated but noncapillary vessels between the two systems. In either case, the flow of blood is directly from artery to vein, bypassing the capillary network. The vessels composing the fistulae, as in our two cases, are arranged in varying numbers of coils which impinge on the cerebral tissue as they grow.

* References 9-11.

It has long been known that the presence of an arteriovenous fistula anywhere in the body may cause alterations in the circulation of a degree roughly proportional to the size of the fistula. Steinheil,† in 1895, described clinical cardiac enlargement in reporting the first case of cerebral arteriovenous fistula in an adult, and Blank,‡ in 1910, reported cardiac hypertrophy in an autopsied case.

Holman,[13] LaPlace,[14] Elkin and Warren,[15] and others have carefully described the clinical effects of traumatic arteriovenous fistulae on the cardiovascular system. These authors point out that the larger fistulae are frequently associated with cardiac enlargement and increased cardiac output. The pulse pressures were widened as a result of lower diastolic levels. Occasionally electrocardiograms showed tachycardia with suggestion of myocardial damage. These clinical changes were corrected with occlusion of the fistulae.

Epstein and co-workers[16] studied seven soldiers with traumatic arteriovenous fistulae by cardiac catheterization. Occlusion of the shunt in their cases brought about the following changes: (*a*) rise in diastolic pressure, resulting in a narrower pulse pressure; (*b*) slower pulse rate; (*c*) fall in cardiac output in those cases in which it had been elevated, with rise in the peripheral vascular resistance; (*d*) slight fall in right ventricular diastolic pressure in two patients, and (*e*) fall in pulmonary-artery pressure in those cases in which the cardiac output fell. They confirmed the clinical impression cited above that there is a correlation between the size of the shunt and the degree of increase in cardiac output.

They feel that the large arteriovenous fistula, by bypassing the capillary bed, contributes to the lowered peripheral vascular resistance. This then results in an increase in cardiac output, probably because of three factors: (*a*) lowered pressure in the carotid sinus and aortic arch areas causing increased heart rate; (*b*) decreased pressure in the aorta against which the left ventricle must work, and (*c*) increased inflow to the right ventricle. The prolonged increased cardiac output results in dilatation of the cardiac chambers and, in some cases, in eventual cardiac failure.

Shenkin and co-workers[17] have shown that the previously described clinical and physiological changes in the circulation noted in cases of traumatic arteriovenous fistulae apply also to congenital cerebral arteriovenous aneurysm. Both of their patients had lowered diastolic systemic pressures and cardiomegaly demonstrable by x-ray. One had an electrocardiogram suggestive of myocardial damage. The cerebral blood flow, determined by the nitrous oxide method, was approximately three times normal, and the cerebral vascular resistance was one-third normal. Cardiac output in their cases, as determined by the ballistocardiographic method, was increased one-third over the expected normal.

No reports could be found in the literature of cardiomegaly and death in the newborn period associated with arteriovenous fistula in the brain or elsewhere. Jaeger and Forbes[11] have reported a single case of a child who was felt to have clinical congenital heart disease of undetermined type between the ages of 15 and 27 months, at which time the clinical diagnosis of cerebral arteriovenous aneurysm was made. This diagnosis was verified at autopsy at the age of 4 years. The heart was enlarged but was structurally normal. This case, the youngest on record to date with cardiac complications, was reported and discussed purely from the point of view of the neurological disturbance.

Definite clinical diagnosis of this condition probably can not be made in the newborn period. It should be kept in mind, however, as a possibility in the differential diagnosis of infants and children with gross cardiomegaly. Theoretically, it would seem that the diagnosis could be established by the discovery of a machinery-type continuous murmur on placing a stethoscope over the scalp. Cursory auscultation of the scalp in our second case failed to reveal such a murmur.

† Cited by Cushing and Bailey.[12]

‡ Cited by Cushing and Bailey.[12]

SUMMARY

Clinical and pathological data on two newborn infants with large cerebral A-V aneurysms are presented.

Gross cardiomegaly, cyanosis, and other evidences of congestive failure suggested the clinical diagnosis of congenital heart disease in both instances. At autopsy a large heart without structural abnormality was found in each case.

A brief review of the literature on congenital cerebral A-V aneurysms and a discussion of their circulatory effect is presented.

It is proposed that congenital cerebral A-V aneurysms should be included in the differential diagnosis of newborn infants with marked cardiomegaly and congestive failure.

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Serum Pigment Studies in Newborn Infants

I. Erythroblastosis Fetalis

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Serum pigments in infants with erythroblastosis fetalis have been studied spectrophotometrically by Abelson and Boggs [1] and by Waters and co-workers.[2] Recently Boggs and Abelson [3] have determined alkaline hematin levels in erythroblastosis fetalis in an effort to evaluate the severity of the disease. A major difficulty associated with spectrophotometric studies of serum is that withdrawal of blood and separation of plasma or serum is practically always attended by hemolysis to some degree. Hemoglobin thus released may contribute significantly to light absorption, particularly in the region of 415 mμ. We have overcome this difficulty by separating the hemoglobin from other serum pigments by paper electrophoresis, following which spectrophotometric analyses have been done without the interference of hemoglobin.

ANALYTICAL METHODS

Multiple blood specimens were collected for analysis (*a*) from the umbilical vein at the time of delivery immediately after pulsation had ceased, (*b*) from the umbilical or femoral vein before, during, or after replacement transfusion. After clotting had occurred, the sample was centrifuged and the serum promptly removed and stored at 4 C until analyzed, which was usually within 24 hours after collection.

Serum bilirubin levels were determined by the method of Hsia and co-workers.[4]

Light absorption spectra were determined on a Beckman model B spectrophotometer with the sensitivity control at position "3." Sera were usually diluted 1 : 50 with 0.9% NaCl solution; the specimens with high bilirubin levels were diluted 1 : 100.

Filter-paper electrophoresis was carried out on Whatman 3 mm. filter paper 1 in. (2.5 cm.) wide and 15 in. (38 cm.) long. The strips were supported in a horizontal position by a large number of small plastic points in an airtight compartment which also contained the anode and cathode electrodes and buffer solutions. Separations were performed in the refrigerator at a buffer solution temperature of 9-11 C. With certain exceptions which will be pointed out later, 0.08 M barbital (Veronal) buffer at pH 8.6 was used. In order to avoid turbidity it was necessary to use freshly prepared buffer solutions, and each solution was used for only one group of electrophoretic separations in which light-absorption determinations were carried out. In all cases, the sample of serum was applied to paper which had been previously moistened with buffer and allowed to equilibrate in the apparatus for at least 30 minutes. Under these conditions a clear separation of the major serum proteins was obtained after six or seven hours at a potential of 400 volts.

The separated serum proteins were stained with bromphenol blue by the technique of Kunkel and Tiselius.[5] The benzidine reagent and hydrogen peroxide solutions which were used to identify hematin pigments were prepared according to the method outlined by Ham.[6]

Hemoglobin solutions were prepared by the method of Drabkin.[7] Fetal hemoglobin was identified by its resistance to alkaline denaturation.[8]

RESULTS

1. Light-Absorption Spectra of Diluted Sera Obtained from Infants with Erythroblastosis Fetalis

Light-absorption spectra were determined in samples from 18 patients with erythroblastosis fetalis in whom a total of 28 re-

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From the Division of Pediatrics, University of Tennessee College of Medicine, the John Gaston Hospital and Le Bonheur Children's Hospital.

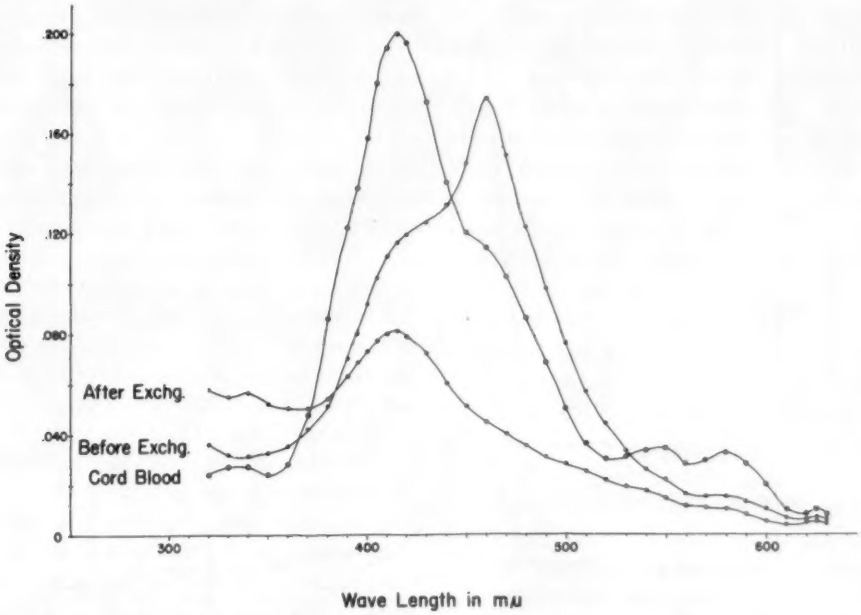


Fig. 1.—Light-absorption spectra of diluted sera (1:50 dilution) from an infant with erythroblastosis fetalis.

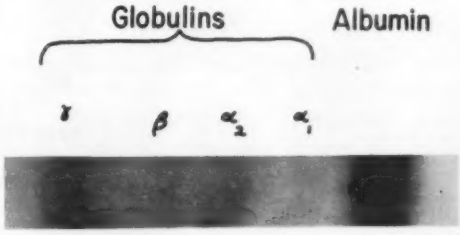
placement transfusions were performed. Figure 1 shows the typical spectra of sera obtained from cord blood and from samples of blood immediately before and after replacement transfusion in a case of erythroblastosis fetalis due to Rh incompatibility. A high light-absorption peak is noted at 415 mμ in cord blood, and prominent absorption peaks at 415 and at 460 mμ in the sample obtained before replacement transfusion. Less prominent peaks are frequently demonstrable at 325, 500, 540, 575, and 623-625 mμ. Following replacement transfusion the only absorption peak is at 415 mμ.

In general, the degree of light absorption at 460 mμ is closely related to the degree of bilirubinemia. In samples containing large amounts of pigments absorbing light in the 405-415 mμ area, a discrete peak at 460 may not be demonstrable, owing to the overlapping effect of pigments with peak absorption in the shorter wave lengths. The height of the peak at 405-415 mμ generally bears a direct relation to the severity of the disease as determined by other laboratory and clinical methods, but in our experience this is inconsistent. The absorption peak in the 405-415 mμ area in the majority of cases was at 415 mμ, in the remainder at 405 mμ.

2. Light Absorption Spectra of Pigments Associated with Various Serum Proteins

The major serum proteins were separated by paper electrophoresis in duplicate, 0.08 cc. samples of sera obtained from an infant with severe erythroblastosis being used. One of the duplicate paper strips was stained with bromphenol blue to locate the serum proteins. Figure 2 shows such a stained strip. The second of each of the duplicates was sectioned while wet so that each section contained one of the five major proteins. Each

Fig. 2.—Position of major serum proteins after electrophoresis on filter paper; stained with bromphenol blue.



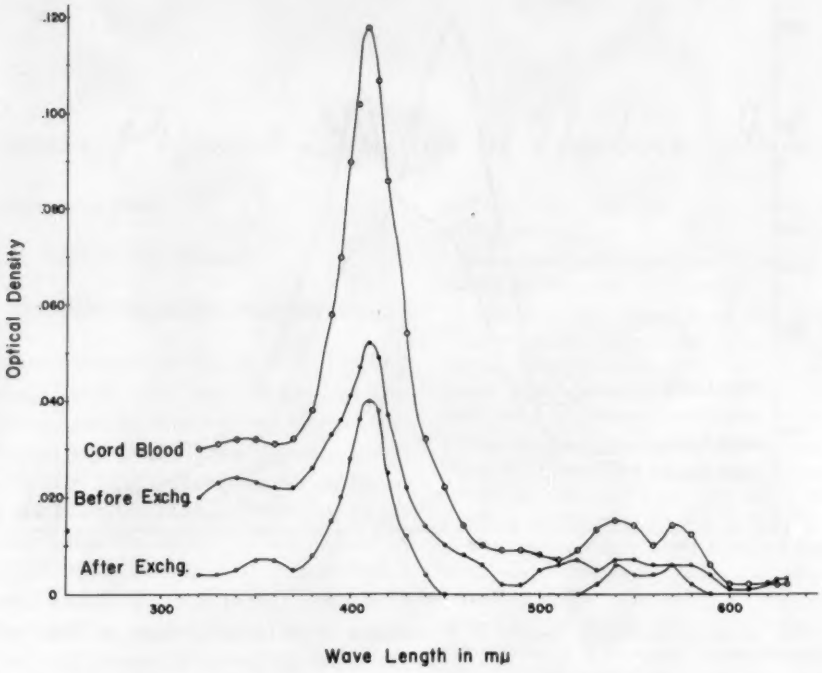


Fig. 3.—Light-absorption spectra of eluted beta globulin fractions.

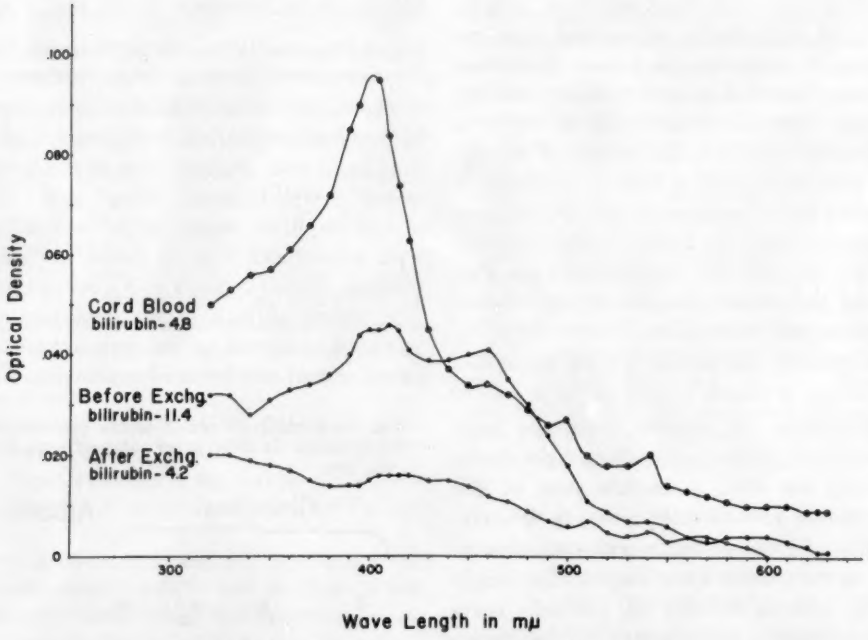


Fig. 4.—Light-absorption spectra of eluted albumin fractions.

of these fractions was eluted from the paper in separate tubes containing 4 cc. of 0.9% NaCl. Light-absorption curves from 325 to 630 mμ were then determined on each of the eluates.

Significant light-absorption peaks in the range studied were found in the eluates of the albumin and beta globulin only. Figure 3 shows the light-absorption curves of the beta-globulin fraction of cord blood and of samples taken before and immediately following exchange transfusion. The absorption peak at 415 mμ is highest in cord blood and lowest in the sample obtained following exchange transfusion. The addition of small amounts of fetal or adult hemoglobin to this serum before electrophoresis resulted in an increase in the degree of absorption at 415 mμ in the beta-globulin area. Hemoglobin not mixed with serum had the same apparent mobility on filter paper as beta globulin when electrophoresis was carried out as described above. Furthermore, the absorption spectra of solutions of oxyhemoglobin[9] resemble very closely those of the eluted beta globulin fractions.

The absorption spectra of the eluted albumin fractions of these three samples of sera are shown in Figure 4. In cord blood there is a high peak at 405 mμ with minor peaks at 460, 500, and 540 mμ. Light absorption at 405 mμ is greatly reduced before the exchange transfusion, and at this time a discrete absorption peak at 460 mμ is apparent. Following exchange transfusion there are no definite peaks.

Similar results have been obtained in three additional cases of erthroblastosis fetalis.

3. Experiments Employing the Benzidine Test for Hematin Pigments

Paper electrophoresis was performed in duplicate on 0.02 cc. quantities of sera obtained from cord blood and blood obtained prior to and following replacement transfusions in a case of severe erythroblastosis. Following electrophoresis the strips were air dried at room temperature. One of the duplicate strips was stained with bromphenol blue. The dye from successive $\frac{1}{10}$ in. segments of the stained paper strip was eluted for one hour in tubes containing 4 cc. 0.1 N NaOH, following which relative dye concentrations were determined in the Beckman Model B spectrophotometer at a wave length of 590 mμ. The relative dye concentrations in each successive $\frac{1}{10}$ in. strip were then plotted on graph paper, revealing the distribution of the major serum proteins. The second of each duplicate was cut in $\frac{1}{10}$ in. segments, and each segment was placed in a tube containing 1 cc. of benzidine reagent and 1 cc. of 0.6% hydrogen peroxide for one hour. The color which developed in each tube was determined spectrophotometrically at 590 mμ after the addition of 5 cc. of 20% acetic acid. Figure 5 shows the distribution of serum proteins as determined by eluting the bromphenol blue and the distribution of the benzidine-positive compounds in this series of samples. Since the serum proteins in each sample were found to be located at the same relative distances from the respective origins, only one bromphenol-blue-elution curve has been shown in Figure 5. The relative concentrations of the benzidine-positive compound in the beta globulin area vary considerably and in this series of samples bear no apparent relation to the clinical status of the infant.

A benzidine-reacting compound in the albumin area was found in cord blood and also before the first and second replacement transfusions, but not immediately following the replacement transfusions. This compound was absent 24 and 48 hours following the second replacement transfusion.

In a second series of experiments employing the benzidine test, 0.02 cc. samples of sera were separated by paper electrophoresis, following which the strips were air dried at room temperature and lightly sprayed with benzidine reagent and with hydrogen peroxide. A benzidine-positive compound was found in the albumin area of sera obtained prior to 28 replacement transfusions on 18 infants. The compound was either qualita-

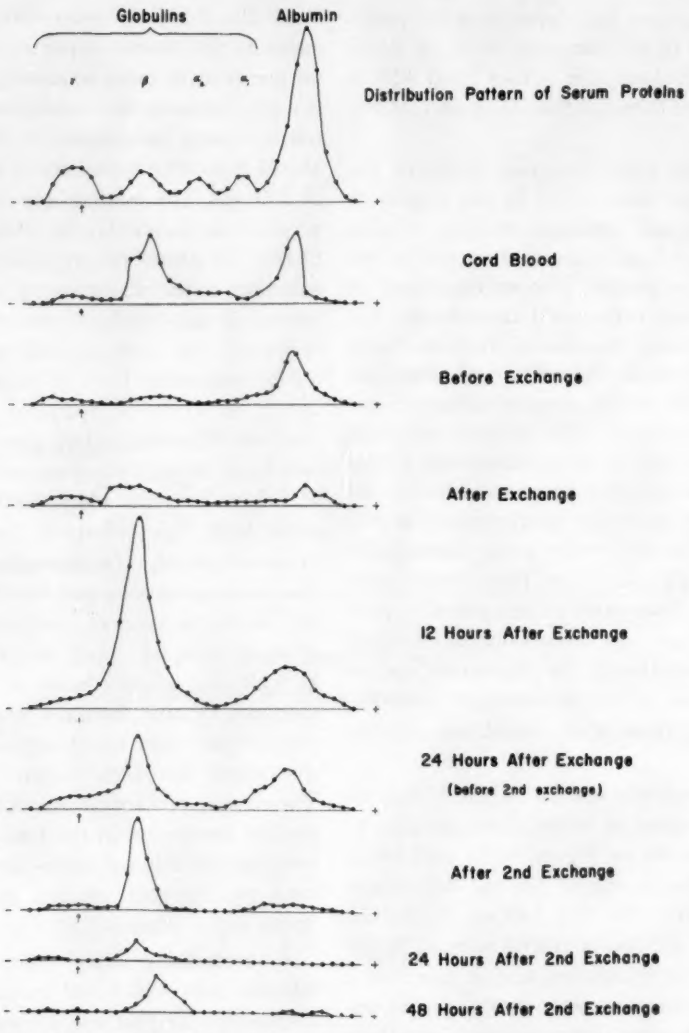


Fig. 5.—Distribution of benzidine-positive compounds in sera from an infant with erythroblastosis fetalis compared with distribution of serum proteins (top) after electrophoresis on filter paper.

tively reduced or was absent following the transfusions.

Analyses of samples of cord blood of 40 full-term apparently normal infants by this method revealed the presence of a benzidine-positive compound in the albumin area in approximately one-half the samples analyzed. The compound disappeared from the peripheral blood of these infants within 12 or 24 hours. A positive benzidine test in the area of beta globulin was obtained in practically all samples analyzed.

COMMENT

I. Identity of Pigments

By the techniques described three distinct serum pigments have been demonstrated in association with hemolytic anemia due to erythroblastosis fetalis, two of which migrate electrophoretically with albumin and one with beta globulin. The light-absorption peaks of diluted samples of sera represent a summation of these pigments.

Because of the similarity of the light-absorption spectra of the pigment found in the

eluted beta globulin fraction to the spectra of solutions of oxyhemoglobin, this pigment is believed to be oxyhemoglobin. Further evidence is that the electrophoretic characteristics of fetal or adult hemoglobin are such that when mixed with specimens of sera of newborn infants or when analyzed alone they migrated to the same position as the beta globulin under the experimental conditions employed. We have observed that the electrophoretic mobility of hemoglobin in sera of older infants and children usually resembles more nearly the mobility of alpha ^{2}-globulin than of beta globulin. Occasionally the hemoglobin fraction of sera obtained following replacement transfusion from infants with erythroblastosis fetalis exhibits this electrophoretic characteristic. Factors governing the mobility of hemoglobin in serum-hemoglobin mixtures have not been determined as yet.

The light-absorption peak at 460 mμ in diluted samples of sera and in the eluted albumin fraction is believed to be due to the presence of bilirubin, which, under the experimental conditions employed, is associated with the albumin fraction of serum. An absorption peak at 460 mμ is characteristic of bilirubin-protein complexes in aqueous solution.[10] On the unstained completed electrophoretic strip, the yellow color of bilirubin is readily visible in the area of albumin. Electrophoresis employing 0.6 M phosphate buffer at pH 7.35 yields similar results.* The eluted albumin fractions (electrophoresis in barbital [Veronal] buffer, pH 8.6) of a limited number of samples of sera containing high levels of indirect bilirubin have been analyzed by the van den Bergh test. It was found that from 65% to 85% of the calculated amount of bilirubin originally added to the strip could be recovered in the albumin eluate. Furthermore, it continued to behave as the indirect type pigment. It is believed that the fraction of bilirubin not recovered in the albumin eluate may be accounted for by irreversible adsorption on the paper, partial oxidation to biliverdin, or complex formation with certain of the globulins in such small quantities as to preclude detection spectrophotometrically. Indirect bilirubin-globulin complexes have been adequately demonstrated by other methods of study.[10]

The absorption peak at 405 mμ demonstrable occasionally in the samples of diluted sera and in the albumin eluates may be attributed to the presence of a hematin-albumin complex, methemalbumin.† Lemberg and Legge,[13] in a comprehensive review of hematin metabolism, list a number of pathologic conditions in which hematinemia (probably methemalbuminemia) has been demonstrated. This list includes hemolytic anemias, nocturnal hemoglobinuria, icterus neonatorum, pernicious anemia, malaria, septicemia, severe liver disease, and cases of poisoning due to certain drugs. We have been able to demonstrate methemalbuminemia in a limited number of cases of sickle-cell anemia.‡ The possibility that certain characteristics of the light-absorption spectra of sera from infants with erythroblastosis might be due to methemalbumin has been suggested by Smith § and by Abelson and Boggs.[1] Methemalbumin is characterized by a major absorption peak at or near 405 mμ and minor peaks at 500, 540, and 623 mμ.[14] We have been able to demonstrate a light absorption peak at 623 mμ in relatively few samples of sera. When present, it is found in the albumin eluate. The other light-absorption peaks which characterize this pigment are demonstrable in the albumin eluates as shown in Figure 4. The observation that samples of diluted sera may display absorption peaks at either 415 or 405 mμ or both, apparently depends upon the relative amounts of hemoglobin (415 mμ) and methemalbumin (405 mμ) in the sample.

The positive benzidine reaction obtained with the albumin fraction serves only to identify a compound with peroxidase activity. This property is possessed to varying degrees by hematin and hematin-protein complexes.[15] The benzidine test alone would,

* Tuttle, A. H.: Unpublished data.

† References 11 and 12.

‡ Tuttle, A. H.: Unpublished data.

§ In discussion of Reference 1.

therefore, not exclude the presence of hematin-containing enzymes, such as catalase, in the albumin eluate.

Methemalbumin is believed responsible for the positive benzidine reaction obtained in the albumin area of the separated samples of cord blood from normal infants. The presence of hematin in normal cord blood has been previously reported.[16] Examination of completed and benzidine-stained electrophoretic records of equivalent amounts of serum indicates that the methemalbumin levels in erythroblastotic infants are much higher than in normal infants.

II. Significance of Hemoglobinemia and Methemalbuminemia

The amount of free hemoglobin in the samples which we have studied is not consistently related to the clinical condition of the infant (Fig. 5). It is likely that a closer correlation might be established by taking special precautions to avoid hemolysis during withdrawal of the blood and separation of the serum. Unusual fragility of erythrocytes of newborn infants [17] and the fact that considerable hemolysis of donor erythrocytes would be expected to occur during the procedure of a replacement transfusion are factors, in addition to intravascular hemolysis, which would influence the amount of measurable serum hemoglobin in infants with erythroblastosis.

Methemalbuminemia in erythroblastosis fetalis is to be expected, since the compound has been demonstrated in other hemolytic anemias.[18] Hematin released as a result of intravascular hemolysis, or when injected intravenously, combines quickly with albumin to form the relatively stable complex, methemalbumin.‖ In erythroblastosis fetalis, the hematin fraction of methemalbumin is undoubtedly derived chiefly from hemoglobin released during intravascular hemolysis. The demonstration of methemalbumin in cord blood of normal infants introduces the possibility that degradation of hemoglobin in the placenta as the fetus approaches term may also contribute to the total amount of hematin available for complex formation with albumin.

The experiments of Rosenfeld and Surgenor [14] and of Herman and Davorin [18] indicate that methemalbumin formation takes place readily until the molecular ratio of hematin to albumin exceeds 2:1. It is likely that the total capacity of albumin to combine with hematin is exceeded only when the ratio of 4 moles of hematin : 1 mole of albumin is exceeded. Hematin appears to be selectively combined with albumin in preference to other serum proteins. Combination of hematin with alpha ^{2}-globulin may occur, but only after the albumin fraction is "saturated."[18] We have not found evidence of hematin-alpha ^{2}-globulin complex formation in the cases of erythroblastosis fetalis which we have studied. For this reason, we assume that saturation of the albumin fraction with hematin has not occurred and that the hematin present in sera of these infants exists entirely as methemalbumin.

The processes by which methemalbumin is metabolized are largely unknown. The experiments of London [19] establish the fact that hematin injected into experimental animals is converted, at least in part, to bile pigment. The elimination of hematin, presumably as bile pigment, appears to depend upon normal liver function.[20]

Since the relative affinity of tissue proteins for hematin has not been studied, factors governing extravascular distribution of hematin are unknown. Spectrophotometric studies of brain sections ¶ and of brain extracts # of infants dying with kernicterus have not revealed the presence of hematin in the brain. It should be remembered, however, that bilirubin in such preparations might obscure the presence of hematin when analyzed spectrophotometrically. Furthermore, in preliminary experiments we have accumulated evidence that hematin and bilirubin may be extracted separately from serum protein complexes by altering the pH at which the

‖ References 11 and 12.

¶ Weech, A. A., in discussion of Reference 21.

References 2 and 22.

procedures are carried out. The fact that hematin has not been demonstrated spectrophotometrically in brain extracts therefore does not necessarily indicate that it is absent in the brain tissue.

Kernicterus may develop in nonhemolytic icterus [23] in which there is no evidence of hemolytic anemia. Methemalbuminemia resulting from excessive intravascular erythrocyte destruction would therefore not be anticipated. High levels of indirect bilirubin in the serum in this condition are believed to result from an inability of the liver to excrete a normal load of bilirubin. Since methemalbuminemia may occur in certain forms of liver disease,[13] one must not overlook the possibility that functional subnormality of the liver responsible for hyperbilirubinemia in cases of nonhemolytic icterus might also result in methemalbuminemia.

The toxicity of hematin or of methemalbumin has not been studied adequately in the human. For this reason, the direct effects of methemalbuminemia upon the newborn infant cannot be evaluated at this time.

Certain possible indirect consequences of elevated serum levels of this compound in erythroblastosis fetalis deserve attention, particularly regarding the effect of hematin upon the mechanisms of serum transport of bilirubin and upon factors governing the extravascular distribution of bilirubin. Both hematin and bilirubin form serum protein complexes and are apparently transported in this manner. Furthermore, the molecular structure of the two compounds is quite similar. For this reason it is not unlikely that they occupy identical sites on the protein molecules with which they tend to combine in complex formation. The amount of either bilirubin or hematin with which a given quantity of protein could combine would therefore depend upon the degree to which the protein was "saturated" with the other compound, provided the protein has the same affinity for bilirubin and hematin. Our preliminary studies along these lines indicate that serum protein-hematin complexes are relatively more stable than corresponding bilirubin complexes. It is therefore suggested that the extravascular distribution of bilirubin may depend, among other factors, upon the degree to which the "bilirubin-binding" capacity of serum proteins is modified by the presence of available hematin.

In other phases of study of erythroblastosis fetalis the biochemical interrelationship between bilirubin and hematin has received attention. The similarity in molecular structure of bilirubin and hematin led Najjar [24] to postulate that the two compounds might compete for protein-complex formation. Since the activity of certain respiratory enzymes in the brain (cytochrome systems) depends upon the presence of the prosthetic group, hematin, he suggested that the deleterious effects of hyperbilirubinemia in erythroblastosis fetalis might be the result of a competition between bilirubin and hematin for complex formation with the protein moiety of the enzymes. Replacement of hematin by bilirubin would interfere with the respiratory functions of the cytochrome systems in the brain. Actual depression of respiratory activity of isolated living sections of brain by the addition of bilirubin to the system has recently been reported by Day.[25] That this effect was the result of interference in the function of cytochrome enzymes is indicated by the fact that the addition of cytochrome C to the system resulted in a reversal of the effects of bilirubin.

SUMMARY AND CONCLUSIONS

Serum pigments in erythroblastosis fetalis have been studied by filter-paper electrophoresis and spectrophotometry.

Light-absorption curves of samples of diluted sera obtained from infants with erythroblastosis are similar to those obtained by other investigators.

The configuration of these light-absorption curves appears to depend upon the presence of at least three pigments in the sera, i. e., hemoglobin, bilirubin, and methemalbumin.

Under the conditions of the experiments hemoglobin exhibited an electrophoretic mobility similar to that of beta-globulin.

Hematin and bilirubin exhibit electrophoretic mobilities similar to albumin and probably are attached to albumin as hematin-albumin (methemalbumin) and bilirubin-albumin complexes, respectively.

The possible significance of methemalbuminemia in erythroblastosis fetalis is briefly discussed.

Methemalbumin may be a constituent of cord blood of normal full-term infants.

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Electrophrenic Artificial Respiration in the Newborn

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The production of artificial respiration by means of electrical stimuli to the phrenic nerve has been known for more than 150 years. Its use in the treatment of newborn infants had its beginnings in modern times with Israel.[1] He gives a complete summary of the literature, beginning with Hufeland, in 1783. In his own series he treated six asphyxiated newborn infants who survived. His means of electrophrenic respiration was an induction coil. It is not possible to estimate the strength of the current that he applied, as he states only the distances between the primary and secondary coils.

Cross and Roberts[2] reported a series of 29 asphyxiated newborn infants, of whom 25 survived. They made measurements of the currents required and correlated these observations with the severity of asphyxia. They found that the severer the asphyxia the greater the current that was required. It has been noted uniformly by all observers that the currents required to produce a respiratory response in the newborn infants are appreciably greater than in the adult. The reasons for this difference may be divided into two groups. First, those due to anatomical differences, and, secondly, those due to asphyxial changes.

The anatomical differences are mainly in the nerve fibrils. Hursh[3] found that the diameter of nerve fibril is smaller in young animals than in adults, and the conduction velocity correlates in a straight-line pattern with the outside diameter of the fibers. Erlanger and Gasser[4] demonstrated an inverse relationship between threshold and rate of conduction of their neurofibril preparations. They found that the greater the conduction rate, the lower the threshold value. From these findings one might assume that the threshold for a given nerve would be higher in a young infant than in the adult.

The asphyxial changes are best described by Lorente de No,[5] who found a gradual lowering of membrane potential in the presence of a lowered oxygen tension or an increased carbon dioxide tension and, consequently, an increasing threshold value. Therefore, in the presence of asphyxia one would expect that a greater current would be required to produce an adequate response. This is substantially the finding of Cross and Roberts,[2] in their measurements of current.

One further fact not related to nerve physiology remains. Skin resistance is perhaps higher in newborn infants than in

Sanborn electrophrenic respirator in use. Note abdominal bulge from contracting diaphragm.

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TABLE 1.—*Apnea (Fourteen Cases Survived)*

Case	Mat. Hist.	Narcotic Anesthesia	Type Delivery	Birth Wt., Lb.-Oz. (Gm.)	Indic. for EPR.	Age Treated, Min.	Clin. Cond. of Infant	EPR.	Other Resusc.*	First Breath	Result
W1	Duipara; age 24	Meperidine, 100 mg., 15 hr. prepartum	Precipitate	9-10 (4325)	Apnea	10	Flaccid, cyanotic; occasional gasping pulse 60	Sanborn; right side, response and audible inspiration sucking; color pink after 12 EPR. breaths; excellent	None; tracheal catheter	10 min.; 60 sec. after EPR.	Discharged good condition after 4 days
J2	Nullipara; 28½ hr. labor	Saddle block	Single footling breech; br. extraction; episiotomy	6-1 (2758)	Apnea	3	Cyanotic decreased mus. tone; made 2 spontaneous gasps; pulse 100	Sanborn; vigorous insp. at 70; auditory inspiration sucking; color improvement immediately	None; tracheal catheter	5 min.; 2 min. after EPR.	Discharged in 4 days
B3	Age 24; tertipara	Morphine, 1/6 grain, 2 hr. prepartum	Spontaneous	8-12 (3970)	Apnea	2	Cyanotic; decreased muscle tone; no respiration effort; Pulse 100	Sanborn; good response at full volt	None; tracheal catheter	4 min. cry; regular respiration 6 min.	Discharged in 4 days
J4	Nullipara; age 17	Morphine, 1/6 grain,25 min. prepartum	Single footling breech	7-1 (3200)	Apnea	2	Cyanotic; no reflexes; no respiratory effort; pulse 60	Goodwin; fair diaphragmatic response; strong brachial plexus resp.	None; PE airway	5 min.	Discharged in 5 days
W5	Placenta previa; 32 wk. gestation; nullipara	Local	Section	3-14 (1760)	Apnea	4	Mottled cyanosis; no reflexes; flaccid pulse 60	Goodwin; fair response on right side only	None; PE airway	7 min.	Physical and x-ray evidence of atelectasis in lower left lobe
K6	Octipara; age 29	Deep ether 30 min.	No. 2 twin version and extraction	5-15 (2695)	Apnea	2	Slight cyanosis; good muscle tone; no reflexes; pulse 80; well-oxygenated	Goodwin; excellent respiration on contralateral side; strong brachial plexus response	None; PE airway	30 sec.	Discharged in 8 days
S7	Nullipara	Morphine, 1/6 grain, 20 hr. prepartum; morphine, 1/6 grain 1 hr. prepartum; meperidine, 100 mg., 11 hr. prepartum	Narrow outlet; Simpson forceps; Stage 2 for 2 hr.	7-2 (3230)	Apnea	2	Cyanotic; flaccid; pulse 40 and weak; gasped twice	Goodwin; good air exchange	None; tracheal catheter	After 12 EPR. breaths	Inanitation temp. 102 F 3d day; discharged after 10 days

W8	Proteinuria and high blood pressure; age 25	Morphine, ¼ grain 8 hr. prepartum; morphine, ¼ grain, 4 hr. prepartum; chloral hydrate, 2 gm., 6 hr. prepartum	Spontaneous	6-10 (3005)	Apnea	4	Cyanotic; good tone; no spontaneous respiratory effort; pulse 60	Sanborn; good exchange and pulse up within 3-4 breaths	None; PE airway	9 min.	Discharged 5th day
P9	Duipara; age 26	Ether and N_2O_2, 20 min.	No. 2 twin version and extraction	5-10 (2550)	Apnea	3	Cyanotic; no reflexes; flaccid; pulse 60	Sanborn; good exchange; pulse up to 140 in 6-8 breaths	None; PE airway	8 min.	Home in 8 days
M10	Unipara; repeat section	Spinal	Section	7-8 (3400)	Apnea	3	Few gasps; no regular response; pulse 100; muscle tone fair; cyanotic	Sanborn; good response brachial plexus; immediate increase in pulse and color	None; PE airway	6 min.	Home in 4 days
G11	Duipara; age 25	Morphine, 1/6 grain, 4 hr. prepartum	Spontaneous	5-8 (2495)	Apnea	3	Coughed; good tone; cyanotic; pulse 100	Sanborn right side with good and increased response	None; PE airway	4 min.	Home; x-ray showed atelectasis less on treated side
N12	Nullipara	Morphine, 1/6 grain, 1 hr. prepartum	Spontaneous	6-10	Apnea	3	Cyanotic; fair muscle tone; no reflexes; pulse 80	Sanborn; no response; electrode failure	PE airway; positive pressure	10 min.	Discharged in 4 days
W13	Age 18; nullipara	Morphine, 1/6 grain, 4 hr. prepartum	Simpson outlet	8-0 (3630)	Apnea	5	Coughed 1-2 ×; cyanotic; muscle tone fair; pulse 80	Sanborn; right side good response	None; PE airway	8 min.	Discharged in 5 days
C14	Age 23; quartipara	None	Cord prolapsed; breech extraction	7-6 (3345)	Apnea	2	Cyanotic; flaccid; no spontaneous respiratory effort; pulse 50	Sanborn; left side with excellent response; pulse up immed.	None; PE airway	3 min.	Discharged in 4 days

* PE indicates polyethylene airway.

TABLE 2.—*Apnea (Eleven Cases Died)*

Case	Mat. Hist.	Narcotic Anesthesia	Type Delivery	Birth Wt., Lb.-Oz. (Gm.)	Indic. for EPR.	Age Treated, Min.	Clin. Cond. of Infant	EPR.	Other Resusc.*	First Breath	Result
B1	Toxemia; hypertension; nulipara; age 14.	Morphine, ½ grain (3.25 mg.), 3 hr. prepartum; chloral hydrate, 2 gm. 1 hr. prepartum	Kieland forceps rotated from transverse arrest episiotomy	7-13 (3545)	Apnea	2 min.	Flaccid; no reflexes; pallid; pulse 120	Goodwin; fair response but insufficient to produce O_2 exchange	PE airway; pos. pres. intermittent with EPR.	45 min.; gasped 2 hr. regular respirations	Resp. became reg. but after 18 hr. irreg. and died 21 hr.; airlock of no use; subarach. and subdural hematoma; tentorium and falx tears; lungs well aerated
B2	Placenta previa 32 wk.; bleeding with shock	Cyclopentane, 30 min.	Section	3-13 (1730)	Apnea	2 min.	Cyanotic; flaccid; pulse 60	Sanborn; excellent response, right side with improved respiration and voltage cut to 70; hyperventilation with subsequent apnea lasting 2-3 min.†	PE airway; none	3 min.	Severe retraction after 4 hr.; x-ray: atelectasis and enlarged cardiac shadow; alveolar hemorr. rt. lung; left lung atelectasis
B3	Uterine inertia; oxytocin (Pitocin) 8 hr. prepartum	Morphine sulfate, 1/6 grain, 16 hr. prepartum, 1/8 grain, 4 hr. prepartum, 1/6 grain I. V. 20 min. prepartum	Forceful spont. delivery	6-3 (2810)	Apnea	10 min.	Yellow skin, cord and vernix; flaccid; pulse 40	Sanborn; poor air exchange with fatigue and slowing of heart; resusc. for 30 min. without any spontaneous breathing	Tracheal catheter; positive pressure for 10 min. color better and pulse up to 140+; pos. pres. more effective than EPR.	0 min.	Air lock; dead after 45 min.; yellow material in lungs; petech. of asphyxia; no atelectasis
S4	30 wk.; 5 hr. labor; sextipara; age 35	None	Spontaneous 1 hr. after admission	3-3 (1445)	Apnea	2 min.	Cyanotic; flaccid; pulse 60 with no spontaneous respiratory effort	Sanborn; poor resp. both sides; no audible inspiration; mild retraction with EPR.; color improved	None; PE airway	15 min.	Died after 8½ hr.; subarachnoid hemorr. right temporal; tentorial ecchymoses
D5	24 wk.; toxemia; blood pressure 220/160; eclamptic	Morphine, ¼ grain, 2 hr. prepartum; hypertonic glucose	Section	1-2¼ (517)	Apnea	3 min.	Cyanotic; flaccid; pulse 80 to 100	Sanborn; both sides with audible rales; retraction and fatigue	PE airway; pos. pres. exchange better than EPR.	Never effective	Died 2 hr.; atelectasis in both lungs; subarach. hem.; petechial hemorrhages

M6	Nullipara; ruptured membranes 2 wk.	None	Spontaneous episiotomy	3-8 (1590)	Apnea	3 min.	Flaccid; cyanotic; no reflexes; pulse 40	Sanborn; poor response; EPR. 10 min. and still poor condition	PE airway pos. pressure no more effective after EPR.	15 min.	Reflexes returned after 45 min. retraction and weak cry; died 4 hr.; atelectasis scattered both lungs; subarachnoid hemorrhage
C7	Home delivery Chicago Maternity Center	None	Difficult forceps	8-8 (3855)	Apnea	6 hr.	Flaccid; yellow staining; gasping 1-2 × min.; peripheral circulatory collapse	Sanborn; good response both sides; SE	PE airway; positive pressure	Reg. resp. after 30 min. EPR.	Reflexes returned and spont. breathing for 6 hr.; died 12 hr. of age, severe cerebral hemorrhage
W8	Vaginal bleed. 10 days prepartum; quartipara; 26 wk.; age 23	Morphine, 1/6 grain, 2 hr. prepartum	Precipitate on delivery table with membrane intact	1-11 (765)	Apnea	2 min.	Rate 90; no respir. effort; muscle tone and reflexes fair	Sanborn; left lung fair response but fatigue; right lung with good response for 2 min.	PE; pos. pres. stim. with spontan. efforts for 5 min.	6 min.	Breathed very well and color good after 4 hr.; died 5 hr.; blood in peritoneal cavity from ruptured liver; lungs well aerated; brain gyri poorly developed; bilat. subarachnoid hemorrhage
T9	32 wk. nullipara; age 19	Pudendal block	Breech; forceps to head	2-3 (990)	Apnea	2 min.	Very immature; cyanotic; bruised legs and buttocks; pulse 80	Goodwin; poor response with fatigue	PE; pos. pres. when EPR. failed	30 min.	Died after 10 hr.; scattered atelectasis both lungs; subarachnoid hemorrhage
M11	Age 30; sextipara	None	Spontaneous	3-13	Apnea	10 min.	Few spontaneous breaths; put in incubator where noted to be cyanotic and apneic less than 10 min.; foul vernix; retraction of right thorax	Goodwin; excellent response with rapid diminishing cyanosis	None; PE airway	12 min. 2 min. after EPR.	Intestinal obstruc.; 36 hr. surgery 2d day; died 7 days; uncorrected atresia of ileum; lungs normal
A11	Membrane ruptured 2 hr.; vag. discharge 5 hr. prepartum; fetal heart tones good; 4 wk. post-term; tertipara; age 35	Cycloether 30 min.	Section	7-12 (3515)	Apnea	2 min.	Yellow vernix, skin cord, and amniotic fluid; flaccid; pale; pulse 40 and barely audible	Goodwin and Sanborn alternated at intervals with pos. pressure; EPR. unsatisfactory; O_2 exchange better after pos. pressure	PE airway and tracheal catheter; pos. pres. increased pulse to 140	50 min.; irregular gasps	Died in airlock after 4 hr.; atelectasis in both lungs; hyaline membrane

* PE indicates polyethylene airway.
† References 8 and 9.

TABLE 3.—*Atelectasis (Four Cases Survived)*

Case	Mat. Hist.	Narcotic Anesthesia	Type Delivery	Birth Wt., Lb.-Oz. (Gm.)	Indic. for EPR.	Age Treated, Min.	Clin. Cond. of Infant	EPR.	Other Resusc.	First Breath	Result
					Immediate Postpartum Treatment						
H1	Ruptured mem.; 13 hr. labor; posterior pituitary (pituitrin) and no progress	Local	Caesarian section	5-12 (2610)	Atelectasis	4 min.	Cyanotic; good tone; fairly well oxygenated; weak irregular respirations	Sanborn; poor response	None; PE	9 min.	Home 4 days; x-ray at 24 hr. normal
A2	Age 23; tertipara	None	Spontaneous precipitate on delivery table	3-12 (1700)	Atelectasis	15 min.	Minimal cyanosis; retraction; weak cry	Sanborn; left side only with good response; right, 30 min. later	None	2 min.	Premat. nursery; good condition after 2 wk.; home
					Delayed Treatment						
L3	.....	.....	.....	5-2 (2325)	Atelectasis	2 days	Cyanosis, dimin. respiration; pulse 100	Sanborn; only 2-3 good EPR. breaths; nociception most marked	Positive pressure and tr. cath.; immed. post-partum	.....	Home in 2 wk.
R4	Unipara; placenta prev. with bleeding last trimester; 32 wk.	Morphine, 1/6 grain, 1 hr. postpartum; cyclopentane 25 min.	Section	4-0 (1815)	Atelectasis	3 days	Lethargy; cyanosis; diminished response; crys when stimulated	Sanborn; both sides good response; breathing better after procedure	Tracheal cath. in operating room	.....	Home at 5 lb.

TABLE 4.—*Atelectasis (Eight Cases Died)*

Case	Mat. Hist.	Narcotic Anesthesia	Type Delivery	Birth Wt., Lb.-Oz. (Gm.)	Indic. for EPR.	Age Treated, Min.	Clin. Cond. of Infant	EPR.	Other Resusc.	First Breath	Result
B1	32 wk.; 6 hr. labor; quartipara	None	Normal spontaneous	2-8 (1135)	Atelectasis	24 hr.	Moribund; sternal retrac.; cyanosis; atelectasis	Sanborn; feeble contrac.; both sides with fatigue	None	.....	Died 2d day; atelectasis both lungs; subarachnoid hemorrhage
D2	26 wk.; unipara; ruptured membrane 3 days	Ethylene	Spontaneous	1-14 (850)	Atelectasis	3 hr.	Moribund; weak respiratory movements; pulse 80; cyanotic	Sanborn; weak response probably ineffective; only dying gasps	.....	Cried spont.	Died 4 hr.; complete atelectasis both lungs
W3	Rh neg.; tertipara; 30 wk.	None	No. 1 of twins; spontaneous	3-3 (1445)	Atelectasis	12 hr.	Moribund; breathing only with stimulation	Sanborn; good response with fatigue; did not relieve cyanosis	.....	Cried spont.	Died 18 hr.; atelectasis both lungs; hyaline membrane
T4	32 wk. nullipara	Ethylene; secobarbital (Seconal); scopolamine 1/130 grain	No. 1 of twins; spontaneous	4-9½ (2085)	Atelectasis	30 hr.	Failing circula.; mottled cyanosis; condition poor since birth	Sanborn; diaph. contr. ¼; spont. efforts	.....	Cried spont.	Died 2 hr. after EPR.; patchy atelectasis; hyaline membrane and intraventricular hemorrhage of brain
M5	Bleeding in 3d mo.; ruptured membranes 1 mo.; 31 wk.; nullipara	.....	Frank breech forceps	3-4 (1475)	Atelectasis	4 days	Moribund for 3 hr.; no respiratory efforts except when stimulated	Goodwin; fair response both sides; fatigue but able to obtain response 15 min. after heart stopped with inspiratory atelectatic rales	.....	Cried spont.	Died 3 hr.; subdural hemorrhage; patchy atelectasis in both lungs
R6	Unipara	None	Spontaneous	3-12 (1700)	Atelectasis	10 min.	Weak irregular resp.; dusky; pulse 100	Sanborn; both sides with poor response	PE airway	Cried spont.	died 5 days; subdural hemorrhage; atelectasis right lung, left patchy
T7	Nullipara; spontan. delivery at home by father; 26 wk.?	None	Spontaneous	3-8 (1590)	Atelectasis	2 hr.	Cyanotic; tracheal catheter; crys when stimulated	Both sides 5 min.; good response but not sustained	None	.....	Died 20 hr.; atelectasis; aspir. amniotic fluid and early form of hyaline membrane
J8	Age 19; nullipara; spotting postpartum	None	Precipitate in admission room	2 (910)	Atelectasis	5 min.	Cried spont. but irreg. respira. with retr. and cyanosis in oxygen	Goodwin; poor resp. on right side only; remained cyanotic; poor condition on transfer to nursery	None; PE airway	Cried spont.	2d day color, cry, and activity very good; later retraction and shallow response; died suddenly on 8th day; autopsy: patchy atelectasis both lungs; subarachnoid hemorrhage

adults. This resistance would be further increased when vernix is present. Therefore, greater voltage should be required to overcome the skin resistance, and the response would be diminished even further, unless special measures are taken to remove this vernix.

METHODS

Two stimulating devices were used in this study. The first was that described by Sarnoff * and manufactured by the Sanborn Company, of Cambridge, Mass. The pulse generator of this phrenic respirator delivers 60 square pulses per second, 4 msec. broad, to the output tube. The output stage delivers diphasic spikes. The output voltage is variable, but at each setting is of constant voltage. The maximum output is approximately 80 volts. This device when set in the "breathe" position automatically produces inspiration and allows expiration. The rate of respiration can be varied. We used a setting with a rate of about 40 per minute, with equal inspiratory and expiratory phases.

The second stimulating devise was one designed for general laboratory electrostimulation. It is known as the L. T. Neuro-Stimulator (Goodwin) and is manufactured by Lab-Tronics, Inc., of Chicago. It was used because of its wave form of a fixed abrupt rising phase and a falling phase variable from ½ to 10Σ. This device produces a maximum voltage of about 100 volts. The rate of respiration was approximately 40 per minute, with an equal inspiratory and expiratory phase. This respirator was used in 10 instances. In one instance in which both instruments were used, no difference in the response could be noted.

A saline electrode was used in the early stages of the study. It was found that this electrode gradually increased in resistance, and after three weeks of use, there was one failure. The meshes of the cloth covering filled with vernix and, despite the fact that it was carefully wiped with 95% alcohol, gradually increased in resistance. Subsequently, a metal electrode was used which was more easily cleaned. With other factors governing response remaining constant, no difference in response was noted when metal and saline electrodes were compared in experimental animals.

The babies studied were treated at the Presbyterian Hospital premature station and in the Cook County Hospital birth rooms. Atelectasis was generally diagnosed on a clinical basis, though roentgenograms prior to treatment were obtained whenever possible. Apnea was considered to justify artificial respiration if no spontaneous respiration occurred within two or three minutes after birth. In most instances, there was an emergency situation in which we set an arbitrary time limit of five minutes in which to produce an exchange of oxygen. This was in keeping with the practices at these hospitals and the thought in the current medical literature. We are well aware that there are reports of survival of newborn infants without impaired function after periods of 10 or 20 minutes of apnea and insufficient oxygenation. We do not believe, as often stated, that there is always a clear-cut correlation between delayed oxygenation and impaired function.

In order to be sure of a free airway, a special polyethylene intratracheal airway was inserted by means of direct laryngoscopy. The patency of the airway was assured by suction with a smaller polyethylene tube which passed freely through the lumen of the airway. In a few instances, the airway was cleared by means of blind intubation with a woven Nylon shellacked tracheal catheter. Thus, a free airway was always supplied, and oxygen could be administered. Electrophrenic stimulation was not used if the infants were breathing after a minute or two of this treatment.

The infants were treated in the recumbent position, with the head extended and turned 45 degrees to the contralateral side. This was done to increase the working space between the clavicle and the mandible. The electrode was applied to the skin at the motor point of the phrenic nerve on only one side. This enabled us to compare the state of aeration of the treated side with the untreated. In some of the cases in which there was a poor response, both sides were stimulated (Tables). During the later weeks of the study, the infant's arm was raised on the stimulated side and fixed with the forearm under the head. An attempt was made to include the lower cord of the brachial plexus with the phrenic nerve response. This caused an adducting action, raising of the rib cage on that side (but with the arm fixed). Our impression was that this procedure was of some help in resuscitation.

RESULTS

Twenty-five infants were treated in the immediate postnatal period, with apnea as the only indication. Fourteeen of these infants survived (Tables 1 and 2).

Twelve infants were treated with the indication for treatment being atelectasis. Four of these infants survived (Tables 3 and 4).

* References 6 and 7.

COMMENT

The response to electrophrenic stimulation was at a uniform pattern. When the electrode was close to the phrenic nerve in the neck, a strong contraction of the diaphragm was noted by the bulging of the abdomen. In some instances, Litten's sign was present. Suprasternal and intercostal retraction was noted in smaller infants, especially those who showed marked atelectasis at autopsy. Fatiguing of the response was noted frequently in very small premature infants. An initial series of good diaphragmatic contractions was followed in less than two minutes by progressively weaker and less effective ones. No infant survived who demonstrated a fatiguing response. When a good exchange was noted in severely depressed infants, a gradual increase in the diaphragmatic contraction was noted. At times it was possible to maintain a good electrophrenic respiration with less current.

The responses to resuscitation of those infants who had been subjected to anesthesia and analgesia were variable. Among the 14 survivors of the apnea group, only one had neither anesthesia nor analgesia of any kind. In one, the mother had 100 mg. of meperidine (Demerol) 15 hours before delivery. In seven, the mother had morphine from one to four hours before delivery. In six of these, the dosage was ⅙ grain (10.8 mg.) either subcutaneously or intravenously. The other mother received the Strogan.off routine treatment for hypertension (¼ grain [16 mg.] morphine sulfate and 2 gm. chloral hydrate). Exactly what part morphine played in respiratory depression in this series is difficult to state. One might gain the impression that it caused respiratory depression. However, the large number of instances in which the mother received morphine shortly before delivery and the infant breathed spontaneously cannot be reconciled with this theory. Two were delivered by low spinal anesthesia, and one under pudendal block without any other medication. In the two instances of version and extraction of twins, the mothers received ether anesthesia 20 and 30 minutes, respectively, before birth. Both of these infants were well saturated with ether.

The weights of these 14 survivors were, with one exception, 5 lb. (2270 gm.) or more. One infant weighed 3 lb. 14 oz. (1760 gm.). The response in this infant was slower than in the larger infants, and the air exchange did not seem to be as good. It had a difficult time in the premature nursery, becoming cyanotic out of oxygen and requiring a prolonged period of oxygen later. There was roentgenographic evidence of atelectasis on the untreated side.

The onset of spontaneous respiration in these 14 cases was uniformly less than five minutes after treatment was begun. Some of the infants regained normal reflexes and muscle tone within a few electrophrenic breaths. It was not possible to compare these infants with those treated by other methods. They responded at least as quickly, and in the opinion of the majority of observers the electrophrenic-respirator-treated babies seemed to respond more quickly. This was probably due not to a greater respiratory exchange but to a combination of respiratory exchange and improved circulation.

There were 11 deaths out of 24 infants in this series treated for apnea. However, three of these were of less than 26 weeks' gestation and probably previable. Their weights were 1 lb. 2½ oz. (525 gm.), 1 lb. 11 oz. (765 gm.), and 2 lb. 3 oz. (990 gm.), respectively. Electrophrenic respiration was of little effect on these infants. The diaphragm could be seen to contract, but the rib cage was so weak that this contraction was ineffective. Fatiguing of the response was present, and only by means of positive pressure applied to the airway could an adequate exchange of oxygen be effected. Four of this group were premature infants with weights less than 4 lb. These infants appeared to respond somewhat better but failed to survive for various pathological

reasons. Two infants had large tentorial tears and subdural hemorrhages at autopsy. Two had clinical and pathological evidence of severe intranatal asphyxia.

The prognosis in all 11 instances was very bad. In all instances, causes other than postnatal asphyxia can definitely be assigned as the cause of death. It is important to note, however, that in situations where there was evidence of severe damage before delivery, electrophrenic respiration would not produce a contraction of the diaphragm or an adequate exchange of oxygen, whereas positive pressure on the airway did. None of these infants survived, or, when electrophrenic respiration failed, so did other methods.

Twelve infants with the clinical diagnosis of atelectasis were treated. Four were treated within the first hour postnatally. Two survived and two died. One of the deaths occurred on the fifth day, and at autopsy there was found a moderate-sized subdural hematoma. The lungs were well aerated. The other infant died suddenly on the eighth day, when it appeared to be doing very well. It was our impression, however, that the most favorable time for electrophrenic respiration to be effective in treating atelectasis is in the immediate postnatal period. The maximum effect is probably achieved at this time because the infant has not yet become fatigued by his effort at respiration.

The remaining eight infants were treated more than one hour postnatally. Only two of these survived. Both of these infants were more mature, one weighing 5 lb. 2 oz. (2325 gm.) and the other 4 lb. (1815 gm.). This may indicate the inherent greater viability of the heavier infants and corresponds to the experience with the group treated for apnea. It was not possible to produce as effective a diaphragmatic excursion in the more immature infants because of retraction of the rib cage. Whether the survival of these two heavier infants was due to inherent viability or actual relief of atelectasis cannot definitely be stated. It is probably a combination of the two in this instance.

In the six infants who died, there was usually a poor response or an initially good response with fatigue. All but one was less than 3½ lb. (1590 gm.) and in the category in which even a good diaphragmatic excursion was not always accompanied by a good oxygen exchange because of collapse of the rib cage. It was not possible at autopsy to demonstrate any difference in aeration between the treated and the untreated sides. However, in four of the infants who survived after treatment for apnea, we were able to demonstrate by roentgenogram that the stimulated side became aerated more rapidly than the unstimulated side. This could indicate that newborn atelectasis may be favorably affected by electrophrenic respiration in certain situations. Whether by improved techniques and improved stimulating devices this can be applied to situations where it will be life-saving remains for further investigation.

CONCLUSIONS

Thirty-seven newborn infants were treated by electrophrenic artificial respiration. Of these, 25 were treated because of apnea in the immediate postnatal period. There were 11 deaths in this group. Of these, three were considered previable. Of the remainder, five were premature infants of 3½ lb. or less. One had severe cerebral hemorrhage, and two showed evidence of severe prenatal asphyxia.

Twelve infants were treated for atelectasis. There were eight deaths in this group. The four survivals all weighed more than 3½ lb. It was not possible to demonstrate in this series that atelectasis in premature infants was affected by electrophrenic respiration. However, in full-term infants who survived, roentgenograms were taken a few hours postnatally and showed more air on the treated side.

Electrophrenic respiration seems to excel other methods of resuscitation in certain situations. However, because of its lack of versatility, we do not believe it is past the

stage of experimental development, and we therefore do not recommend it for general use.

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Escherichia Coli Diarrhea

An Outbreak Among Infants on a Surgical Ward

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In spite of the extraordinary advances made during the last few decades in sanitation and infant care, diarrheal disease, including epidemic diarrhea of the newborn, still contributes to a considerable extent to the morbidity in this age group. It is obvious that recent information on the etiology, modes of spread, and management must be utilized to the fullest in the control and management of this malady. It is clear that epidemic diarrhea of the infant is not a monoetiological disease. In some outbreaks members of the Salmonella group are responsible for the infection. It is possible that in others a virus, such as that isolated by Light and Hodes,* may be the etiological agent. However, there can be little doubt that certain serogroups of Escherichia coli are responsible for many epidemics. The present report describes an outbreak of E. coli 0111 diarrheal disease among infants on a surgical ward and illustrates the potential danger of the introduction of one of these pathogenic serogroups of E. coli into a ward population.

REPORT OF OUTBREAK

On a surgical ward for infants with a maximal capacity for 10 patients, diarrheal disease made its appearance on Sept. 4, 1954, involving four patients. Within six days, three additional infants developed diarrheal disease. Rectal swabs were taken on Sept. 6 on four of the affected patients and revealed the presence of E. coli 0111 in each of them. Two days later fecal material was obtained from the remaining three patients and again showed the presence of the identical serogroup of E. coli (regarding the serological technique, see Ewing and Edwards [3]). No other pathogenic organisms were isolated. Two additional patients had been discharged before a bacteriological study was undertaken. The pertinent data with regard to these patients are summarized in the Table. The ward was closed to further admission on Sept. 7, 1954. The infection in two infants was severe enough to necessitate transfer to the medical service; the disease was mild in the remaining five cases. Five of the patients were treated with neomycin. All patients recovered from the infection. Follow-up cultures, taken 10 days after the onset of the disease, on five patients failed to reveal the presence of E. coli 0111.

Outbreak of Escherichia Coli 0111 Diarrheal Disease of Infants on a Surgical Ward

Case	Age	Admission to Surgical Ward	Onset of Diarrhea	Surgical Condition
1	3 wk.	9/ 3/54	9/ 4/54	Harelip
2	3 wk.	9/ 1/54	9/ 4/54	Suspected cystic disease of lungs
3	2 mo.	7/29/54	9/ 4/54	Meningocele
4	9 mo.	8/23/54	9/ 4/54	Burn (3d degree)
5	2 mo.	8/31/54	9/ 7/54	Harelip
6	5 mo.	8/31/54	9/10/54	Hemangioma of eyelid
7	5 wk.	9/ 6/54	9/10/54	Fracture of femur

COMMENT

The present outbreak of relatively mild diarrheal disease among infants on a surgical ward was clearly associated with E. coli serogroup 0111, inasmuch as this microorganism could be isolated as the predominant coliform organism from the feces of all

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* References 1 and 2.

seven patients. Among the 130 serogroups of E. coli now known, only a few, notably 0111, 055, and 0127, have been encountered in outbreaks of epidemic diarrhea of infants. More than 25 years ago, Adam [4] described certain biotypes of E. coli, the so-called "Dyspepsiekoli," as causative agents of the disease. Following the pioneer work of Bray,[5] in 1945, the etiological role of certain serological groups of E. coli has been investigated in various parts of the world. The classic studies of Kauffmann [6] on the serology of the Escherichia group has put the identification and classification of these strains on a sound basis. In this country, studies on E. coli diarrhea date back to 1950,[7] and the association of E. coli 0111 and severe epidemic diarrhea of the newborn could be traced back to 1947 by the examination of fecal specimens preserved at low temperature for five years.[8] Investigations into E. coli diarrheal disease of infants have been carried out in Michigan,† Ohio,[11] Colorado,[12] and New York.‡ A recent editorial in the *Journal of the American Medical Association* [14] clearly summarizes the present-day knowledge on this subject. Dr. F. Kauffmann, at the conclusion of a session devoted to E. coli diarrhea during the Sixth International Congress of Microbiology, held in Rome, September, 1953, stated that "the etiological importance of certain serological types of Escherichia coli for epidemic infantile enteritis can not be doubted today."

The recognition of the role of these and other serogroups of E. coli in infantile diarrhea has important practical implications. Sulfonamides and various antibiotics, particularly neomycin, are therapeutically effective. In addition, antibacterial agents may be used in exposed infants and carriers. Clearly, these drugs would be ineffectual in viral diarrhea. That epidemics of this disease can be brought under control by appropriate measures including antibiotic therapy and prophylaxis is evident from the experience of Wheeler and Wainerman.[11] In this connection it is worthy of note that in the outbreak described in this report E. coli 0111 was recovered from two infants 48 hours prior to the onset of clinical manifestations. The source of the present outbreak has not been definitely identified, although Case 1 may be suspected, since this infant apparently had diarrheal disease prior to admission. With a heavy exposure, the incubation period of this disease may be as short as 24 hours.[7]

So far as the prevention of E. coli diarrheal disease of newborn and older infants in nurseries as well as in medical and surgical wards is concerned, it is important that (1) the occurrence during the hospital stay of diarrhea, even if it be mild, be brought to the attention of the physician without delay, (2) bacteriological studies, with particular reference to the pathogenic serogroups of E. coli, be undertaken, and (3) a program for the prevention of the spread of the disease, as recommended by Wheeler and Wainerman,[11] be initiated. Furthermore, as the experience of Rogers and Koegler [15] clearly shows, carriers discharged from one hospital and readmitted to another may initiate an outbreak in the latter institution. Prompt reporting is indispensable for the prevention of the spread of this malady.

SUMMARY

An outbreak of relatively mild diarrheal disease among seven infants on a surgical ward is described, and Escherichia coli 0111 was isolated from all of these patients. The need for the recognition of certain serogroups of E. coli as etiological agents in epidemic diarrhea of newborn and older infants is stressed, and measures for the control of such outbreaks are briefly discussed.

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Cor Pulmonale in Newborn Infants

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Newborn infants with severe atelectasis seldom survive long enough to develop secondary cardiac changes other than dilatation, but in rare instances survival is sufficiently prolonged to permit hypertrophy of the myocardium of the right ventricle, giving the heart the characteristic anatomic configuration of cor pulmonale as seen in older age groups. The clinical findings associated with these secondary changes in the heart may be more striking than those of the primary disease of the lungs, and because the clinical behavior of the atelectasis-cor-pulmonale lesion-complex can so closely simulate that of a congenital malformation of the heart, the correct etiologic diagnosis is often made only after death and examination of the lungs and heart at necropsy. Apparently these facts are not generally appreciated, for in the modern English language literature there are only two reports * which consider in detail the pulmonary heart disease secondary to atelectasis of the newborn.

It would seem that this is a matter of more than academic interest, for there is evidence that the process is reversible and that resolution of the pulmonary lesion may lead to eventual recovery.[2] Also, it is reasonable to expect that currently improved methods of treatment of atelectasis of the newborn will make possible longer periods of survival and that the condition will be observed more frequently than in the past. The object of this report is to direct attention to the atelectasis-cor-pulmonale lesion-complex in newborn infants, and it is based on the pathologic findings in two cases studied at necropsy.

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* References 1 and 2.

REPORT OF TWO CASES

CASE 1.—R. F. A. (U.S.N.H. C.L.N.C. register No. 60668), a 13-day-old Caucasian boy.

Clinical History.—A 19-year-old woman who had come to the term of a previously uncomplicated pregnancy was admitted to the hospital because of premature separation of the placenta. This was successfully treated, and two and one-half days later she was delivered by breech extraction of an infant weighing 3450 gm.

The infant made shallow respiratory motions immediately upon birth, but was deeply cyanotic and had a blowing systolic murmur which was audible over the whole precordial area. Despite continuous oxygen therapy, the cyanosis never fully receded, and there was severe dyspnea followed by slowly progressive enlargement first of the heart and then of the liver. The clinical impression was that this was an example of severe congenital malformative heart disease, and though the cardiac outline was

Fig. 1.—Lung, Case 1. The pleural surfaces of the lung are finely lobulated and marked with scattered petechiae, while the surfaces made by cutting are somewhat everted, poorly aerated, more or less homogenous, and of almost spleen-like appearance.

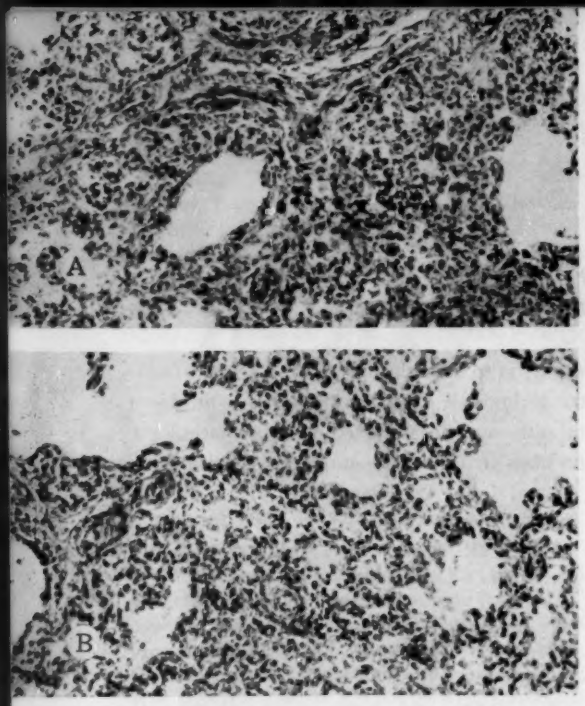


Fig. 2 (*A* and *B*).—Lung, Case 1; reduced approximately ¼ from Mag. × 100. The lung shows a form of severe resorption atelectasis. Observe the loosely knit, heavily vascularized, atelectatic lung parenchyma separating scattered and overdistended alveolar spaces, foci of extramedullary hemopoiesis, and hypertrophic pulmonary arterioles.

not characteristic, the anatomic nature of the malformation was considered to have been that of the so-called "tetralogy of Fallot." Digitalization and other therapy directed toward congestive heart failure were to no avail, and the baby died during the 13th day of life. Roentgenograms, taken early in the course of the disease, were interpreted as showing marked pulmonary atelectasis. Electrocardiographic studies were not done.

Gross Pathologic Findings at Necropsy (U.S. N.H. C.L.N.C. A53-93).—The body was that of a cyanotic infant weighing 3000 gm. The most significant lesions were those of the lungs and heart.

Each pleural sac contained approximately 10-20 cc. of clear serous fluid. The lungs (Fig. 1) were voluminous, dusky gray, smooth, glistening, and marked by an exaggeratedly prominent mosaic of pleural lymphatic vessels. Both lungs were firm and diffusely indurated, rubbery, and of such consistence as to permit their being cut into thin slices. The surfaces made by cutting were smoothly everted (though lobulated after fixation in formalin), reddish-gray, and fairly dry. Dark blood could be expressed from the new surfaces, which were remarkable chiefly because of uniform effacement of the normally spongy alveolar architectural pattern. The bronchioles and pulmonary vessels showed no significant gross abnormality.

The heart was enlarged, weighed 28 gm, and was of the characteristic configuration of cor pulmonale. To best demonstrate the relative volume of the ventricular chambers and the thickness of their walls, it was opened according to a modified Zenker technique.† There was marked dilatation and hypertrophy of the right ventricle and atrium, gross incompetence of the pulmonary valve, and marked dilatation of the pulmonary artery (Fig. 3). The myocardium of the right ventricle ranged from 5 to 7 mm. in thickness, and the volume of the right ventricular chamber was estimated to have been approximately twice that of the left. There was no anatomic evidence of abnormal communication between chambers, endocardial sclerosis, malposition of great vessels, stenosis of the pulmonary artery, anomalous drainage of the pulmonary veins, or other congenital malformation.

Microscopic Pathologic Findings in Necropsy Material.—The most significant lesions were those of the lungs, which showed severe atelectasis of unusual histopathologic characteristics, together with minimal secondary hypertrophic changes of the pulmonary arterioles (Fig. 2). The scattered few alveolar spaces were distended, exaggeratedly outlined by flattened elongated littoral cells, and

† Roessle, R.: Cited by Farber.[3]

Fig. 3.—Heart, Case 1. The heart has been opened after a modified Zenker technique and fixed in formalin in such a manner as to demonstrate the major features of cor pulmonale. The lateral margin of the right ventricle is next to the ruler, and the main portion of the right ventricular wall has been turned to the left to face the camera at right angles, demonstrating the great thickening. Note the tricuspid and pulmonary valves. The hemisection of ventricles and septum shows the relative thicknesses of the walls, and gives some indication of the disparity in volume of the two chambers.

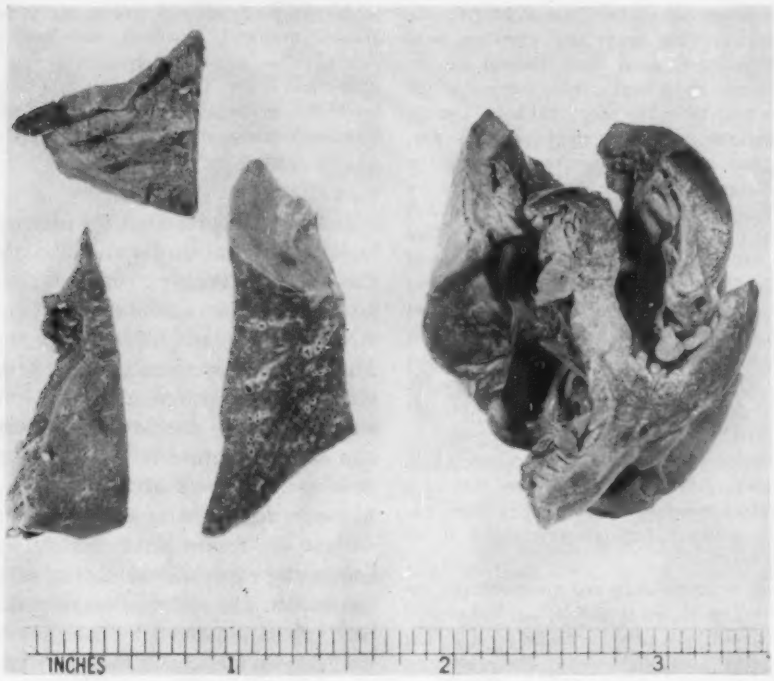
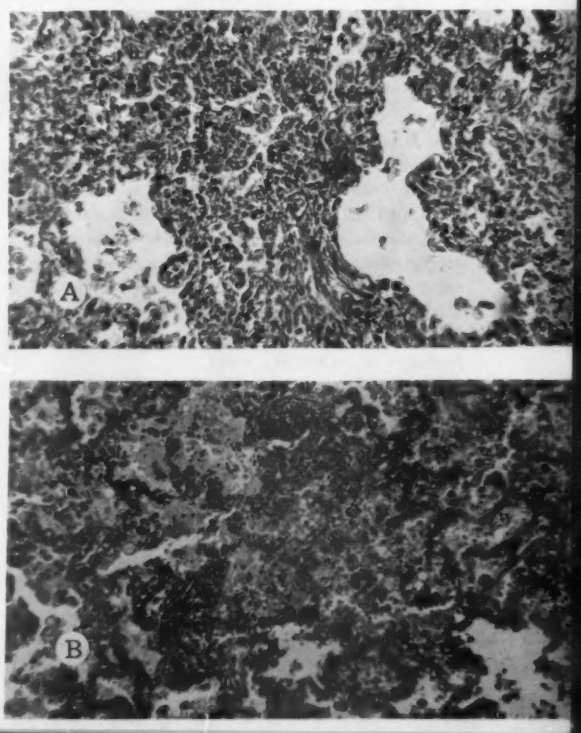


Fig. 4.—Lungs and heart, Case 2. The surfaces made by cutting the lungs are homogenous and atelectatic. The heart, viewed in hemisection from below, is correctly oriented from right to left. Note the dilated relatively thick-walled right ventricle.

sometimes contained large free histiocytes suspended in proteinaceous coagulum. Hyaline membranes were rarely encountered. The alveoli were separated by broad bands or thickened septa of what appeared to be loosely knit mesenchymal tissue, made up for the most part of elongated fibroblasts and heavily vascularized by capillaries distended with clumps of nucleated erythrocytes. A striking feature, particularly in the perivascular adventitial tissues, was that of dense foci of extramedullary myelopoiesis with prominent hemocytoblasts and primitive erythrocytes in varying stages of differentiation. In the majority of microscopic fields, there was no recognizable structural characteristic of the loose interalveolar tissue by which to identify its true nature, but in rare fields in the periphery, it was apparent that it was composed of the septa of collapsed alveoli. The subpleural lymphatic vessels were dilated and empty except for bits of coagulum. Almost all of the pulmonary arterioles showed some degree of intimal thickening, with piling up and digitation of the intimal cells. There was also well-marked medial muscular hypertrophy which was readily demonstrated by Masson trichrome stains.

Case 2.—R. M. W. (U.S.N.H. C.L.N.C. Register No. 69552), a 7-day-old Caucasian girl.

Fig. 5 (*A* and *B*).—Lung, Case 2; reduced approximately ¼ from Mag. × 100. The lungs show marked atelectasis, with intra-alveolar edema, hemorrhage, and histiocytic reaction.



Clinical History.—An infant, born without technical complication after uneventful gestation, was cyanotic immediately upon birth, showed cardiac enlargement, and had a loud systolic murmur which was audible over the entire precordial area. Cyanosis persisted despite continuous oxygen therapy, and there was increasingly severe dyspnea. The cardiac enlargement became progressively more marked during the succeeding days, and it was thought that the clinical picture was that of a severe congenital malformation of the heart—probably of the so-called "tetralogy of Fallot" type. Treatment directed toward congestive heart failure was without significant effect, and the baby died during the seventh day of life. Electrocardiographic studies were not performed, and while roentgenographic studies were performed, the results are not available at this writing.

Gross Pathologic Findings at Necropsy (U.S. N.H. C.L.N.C. A54-3).—The body was that of a cyanotic infant weighing approximately 2600 gm. The most significant findings were those of the lungs and heart.

The lungs were diffusely and symmetrically enlarged, dark grayish-red to purple, and had pleural surfaces marked by a prominent mosiac of lighter gray congested lymphatic vessels. The right lung weighed 30 gm., the left lung 25 gm. Both lungs were diffusely indurated and rubbery in consistence, while the surfaces made by cutting were everted, wet, dark grayish-purple in color, and flecked with myriads of tiny interstitial hematomata (Fig. 4). The normally spongy alveolar pattern was effaced, and the newly made surfaces were relatively smooth. The bronchioles and pulmonary vessels were not remarkable.

The heart was enlarged, weighed 22 gm., and was somewhat globular in configuration. It was opened after a modified Zenker technique to demonstrate a dilated right ventricular chamber of approximately three times the volume of the left (Fig. 4). The myocardium of the right ventricle ranged from 2 to 3 mm. in thickness, but was not otherwise remarkable. There were scattered focal subendocardial hematomata on the superior surfaces of the leaflets of the tricuspid valve, the pulmonary valve was moderately incompetent, and the pulmonary artery moderately dilated. There was no abnormal communication between chambers, endocardial sclerosis, abnormal disposition of great vessels, obstruction of the pulmonary artery, or anomalous drainage of pulmonary veins.

Microscopic Findings in Necropsy Material.—The most significant lesions were those of the lungs, which showed the characteristic histopathologic picture of moderately severe atelectasis with hyaline membrane formation (Fig. 5). Those few open alveolar spaces often contained clumps of erythrocytes and large free histiocytes suspended in proteinaceous coagulum, and several microscopic fields showed aspirated squamous cells and amniotic debris. The subpleural lymphatic vessels were dilated and empty. The pulmonary arterioles showed minimal to moderate thickening of the media but no significant change of the intima.

COMMENT

In both cases presented, the primary pathologic process was that of atelectasis, although the lungs in the first showed an unusual form of the lesion. Under the title "Congenital Alveolar Dysplasia of the Lungs," MacMahon [4] and Kaufman and Spiro [5] have described a similar remarkable atelectatic lesion in almost identical detail, suggesting that its true nature is that of a congenital development defect of lung tissue. Potter,[6] however, regards it as simply a morphologic variant of "resorption atelectasis," and has convincing experimental data to support her contention. The scattered overdistended alveolar spaces separated by band-like areas of exaggerated atelectasis, the prominent foci of hemopoiesis, and the aggregations of dark fibroblastic nuclei simulating foci of lymphocytic infiltration all suggested the possibility of this first case being an example of congenital syphilitic pneumonia, but this was disproved by the facts that there were no compatible lesions in other organs and that in both mother and infant the serologic tests for syphilis were negative. A second possibility, that of this case being a form of interstitial plasma-cell pneumonia, was soon discarded because of the plural cellularity and lack of any actual cytologic evidence of an inflammatory process. It is interesting that in this case the cardiac changes were the most marked.

It is unusual for infants who die of severe atelectasis after surviving for more than a few days to show no evidence of secondary pneumonia.[6] Aside from the suggestion that the antibiotic therapy received by both patients prevented such a complication, there is no explanation for the disparity of these cases. Regardless, it is logical to assume that the prolonged survival due to whatever cause made possible the development of secondary cardiac changes dependent upon al-

terations of some standing in the pulmonary vascular bed.

The mechanism of development of cor pulmonale in atelectasis of the newborn is apparently one of peripheral compression of the capillary vascular bed by collapsed lung parenchyma, with impedence of pulmonary blood flow, dilatation of the chambers of the right side of the heart, and, if this state of affairs is maintained, eventual hypertrophy of the myocardium. Infants who survive these conditions over very long periods of time may develop hypertrophic changes in the pulmonary arterioles, a remarkable case in point being that reported by Mallory,[1] in which an infant survived for six months and at necropsy showed marked pulmonary arteriolar lesions. Death in this condition may be explained by the combined effects of both pulmonary and cardiac failure. Green and Apley [2] have pointed out that in infants the cardiac enlargement secondary to widespread pulmonary disease is reversible and it is possible that some infants with this disease may eventually recover completely.

Perhaps the reason that this condition has not been reported more frequently is that the infant with severe atelectasis either dies in the first days of life before marked anatomic changes in the heart take place or else survives the intermediate period when the changes are best developed. Finally, it is suggested that some cases studied at necropsy may have been erroneously reported under the title "idiopathic hypertrophy of the heart" and that their true nature has gone unrecognized.

SUMMARY

Two cases of a form of cor pulmonale in newborn infants are reported, together with a detailed discussion of the pathologic findings at necropsy and a brief consideration of the pathogenesis of the disease.

Cdr. George E. Meador (MC), U. S. N., Chief of Laboratories at the U. S. Naval Hospital, at Camp Lejeune, gave encouragement and assistance in making available portions of the material used in this report. The members of the Department of Medical Illustration of the Louisiana State University School of Medicine gave assistance in preparation of the photographs.

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Anionic Resin Measurement of Protein-Bound I^{131} in Euthyroid Children

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The measurement of thyroid hormone in the blood has been done more frequently in recent years by several methods: the chemical determination of protein- or serum-precipitable iodine [1]; various measurements of conversion of inorganic to organic iodide, for instance, RBC-plasma ratio,[2] using I^{131} as a tracer, and measurement of butanol-extractable iodine.[3]

We have reported [4] the use of anionic resin for measurement of protein-bound iodine I^{131} in human adult plasma; in the present article we present measurements on euthyroid children. Patients are given I^{131}, and at intervals thereafter blood is drawn. The plasma is then treated with anionic resin. Anionic resin adsorbs inorganic iodide from plasma, leaving organic iodine practically untouched. The measurement is done by scintillation crystal counting of the plasma after it is treated with resin and separated by centrifugation, the resin and supernatant plasma being counted separately. This procedure can be done simply and quickly, and it is regularly reproducible.

Comparable results were obtained by the resin method when compared with the following procedures: (1) Man's method [3] for measuring butanol-extractable iodine in plasma, both protein-bound iodine and inorganic iodide; (2) trichloroacetic acid fractionation of plasma from patients given I^{131} and of plasma seeded in vitro with I^{131}, and (3) separation by dialysis of the free and bound I^{131} in plasma of patients previously given I^{131}, to determine inorganic iodide in the dialysate and organic iodine in the dialyzed plasma.

PATIENTS AND METHOD

Fourteen children were tested. All of them had had poliomyelitis and had been over the acute phase for at least four weeks, during which time they had been in bed. Three patients in respirators had severe paralysis with atrophy and were considerably underweight. They had low basal metabolism rates when out of the respirator, but the rates while in the respirator were then significantly higher but still slightly below normal. The remaining patients had very mild weakness, involving at most only one extremity. At the time of our studies none of these had complete paralysis, and most had striking improvement in muscle function. All 14 were considered euthyroid by the usual appraisal of history and physical examination and by their normal values of thyroid uptake of I^{131} and, when done, blood protein-bound iodine and cholesterol levels and epiphyseal development. The children were given between 10 and 30 μc of I^{131} orally several hours after breakfast.

Read in part before the Society for Pediatric Research, Buck Hill Falls, Penn., May 7, 1954.

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The method of using anionic resin * has been described in detail.[4] One milliliter of a 25% suspension of resin was added to either 1 or 2 cc. of plasma obtained at various hours stated in the Table.

RESULTS

For simplicity the data are expressed as counts per second per cent (c/s%) rather than as microcuries per cent. Corrections were made for the decay of the I^{131} in the samples at the various hours after its administration. For comparison with other data,[4] the data were also corrected to an ideal dose of 100μc I^{131}, to a 100 cc. plasma sample, and to the fraction of the child's weight compared to the ideal adult weight of 70 kg. These corrections were done by use of the following formula:

$$\left[\begin{array}{l}\text{inorganic \& organic iodine, total counts } I^{131} \text{ in plasma, corrected for decay to time of administration} \\ - \left[\dfrac{\text{inorganic iodide counts } I^{131} \text{ on resin}}{0.95,\ \text{the efficiency of the resin}}\right]\end{array}\right] \times \frac{100}{\text{actual dose } I^{131} \text{ in } \mu c} \times \frac{100}{\text{cc. plasma sample used}} \times \frac{\text{patient's wt., kg.}}{70 \text{ kg. ideal adult weight}}$$

$=$c/s% (counts per second per cent) of protein-bound iodine.

As shown in the Table, there was a progressive increase of bound counts detected at the various hours of measurement. At 14 hours, the first measurement time, the c/s% are slightly higher than at 24 hours; this is probably due to the one high reading (22 c/s%; A. R.). Thyroid uptake and c/s% were not done before 14 hours in this group of patients. In an occasional euthyroid child, subsequently tested, we have detected a small amount of binding by this resin method at six to eight hours. Compared with data of 27 euthyroid adults,[4] children appear to release protein-bound iodine earlier and in greater amounts.

COMMENT

The expression of results as counts per second per cent is a quantitative one when standard conditions are used, as expressed in the formula.

This method measures the rate of protein binding, the rate of its release from the thyroid gland into the blood stream as well as the ultimate blood level. The concept of expressing the data as counts per second per

* The resin used was Dowex No. 2 (Dow Chemical Company, Midland, Mich.) and $\times$ 10 cross linkage, 200-400 mesh, preloaded as the chloride form by treating the hydroxy form with saturated NaCl solution. Excess NaCl was removed by washing the resin with distilled water. A suspension of resin was prepared containing 25 gm. of this chloride form of resin in each 100 cc. of water. Some batches of resin had finer mesh material, which did not settle out after five minutes of standing. This was decanted and discarded. The resin suspension was capable of quantitatively binding as much as 50 mg. of iodide. This suspension should be kept in an icebox. Rechecking its iodide-carrying capacity should be done frequently to note any variations in adsorbing power. This can be done by using a plasma sample to which has been added a known amount of I^{131} and carrier iodide. Saturation of the resin with NaCl prevents removal of chloride from plasma, thereby avoiding supernate turbidity and obtaining clean separation after centrifugation.

Plasma-Bound I^{131} of Euthyroid Children and Adults *

Hr. After I^{131}	Observations, No.		Range, C/S %		Mean ± S. E.	
	Children	Adults	Children	Adults	Children	Adults
14	10	..	0-22	....	7.1 ± 2.2	.....
24	3	24	2-10	1-17	6.1 ± 2.3	4.1 ± 1.0
38	11	..	3-27	....	12.8 ± 2.0	.....
48	3	24	14-21	5-25	17.0 ± 2.1	12.2 ± 0.8
62	10	..	14-41	....	22.7 ± 1.5	.....
72	3	25	16-31	4-43	21.7 ± 2.4	17.3 ± 1.8
86	11	..	10-47	....	27.9 ± 3.5	.....
110	11	12	13-85	12-34	44.5 ± 5.8	21.4 ± 2.0

* Data are given for 14 children, aged 4 to 14 years, and 27 adults.

cent is similar to measuring the hormone as micrograms of protein-bound iodine.

The earlier binding and the greater amount in children in comparison with adults might suggest that they bind iodine quicker and in greater amounts (data computed by the formula having been on comparable bases of dose, size of sample, and body weight).

The method could be useful where counting apparatus is lacking or the child is too uncooperative to be measured correctly with an external radioisotope-measuring device. The method has given more reliable results, in our opinion, than tests of blood protein-bound iodine and basal metabolic rate.

SUMMARY

Anionic resin adsorbs inorganic iodide from plasma—the patient having received I^{131}—leaving protein-bound I^{131} (hormone) in the supernate. Counting the two fractions measures the rate of thyroid hormone production.

Results are given on 14 euthyroid children. These are expressed as counts per second per cent.

Children formed hormone more quickly and in greater amounts than adults.

The procedure is done simply, quickly, and reliably.

Mr. James N. Castle, of the Radioisotope Unit, and Drs. E. B. Shaw and Marcia Levin, of the Communicable Disease Department of the Children's Hospital, gave technical help in this study.

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Sydenham's Chorea

I. Evidence of Abnormal Adrenal Cortex Function

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The intimate relationship between chorea minor and rheumatic fever long has been recognized. The criteria of Jones,[1] now accepted as standard for the diagnosis of rheumatic fever, include chorea as a major manifestation. Chorea has been reported to occur in 51% of all rheumatic fever patients during some phase of their illness[2] and as the primary manifestation in 20% to 30%.[3]

Biochemical abnormalities related to adrenal cortex function have been demonstrated to exist in patients with rheumatic fever. These include alterations in the circulating concentrations of certain acute-phase reactants (mucoproteins,* hexosamines,[6] and nonglucosamine polysaccharides[7]) and in the circulating concentrations of adrenal steroids[8] and corticotropin (ACTH).[9] The purpose of this study was to determine whether similar abnormalities exist in patients with Sydenham's chorea.

MATERIAL AND METHODS

The subjects of this study were 30 children seen at the Salt Lake County General Hospital and in the Utah State Rheumatic Fever Clinics during the three-year period from January, 1951, to January, 1954. Each was diagnosed as having Sydenham's chorea on the basis of awkwardness, gross purposeless movements, and a history of emotional lability. In some, carditis was present. In those persons in whom choreiform activity was minimal, the diagnosis was made independently by two or more competent observers.

Blood samples for study were obtained by venipuncture before any therapy was instituted. An aliquot was used for determination of the erythrocyte sedimentation rate (Wintrobe); the remainder was centrifuged and the serum stored in a frozen state until used for the determination of mucoproteins,[10] nonglucosamine polysaccharides,[11] and hexosamines.[12] Plasma levels of 17-hydroxycorticosteroids were determined by the method of Nelson and Samuels.[13] The response of these steroid levels to the administration of exogenous corticotropin was determined in nine of the patients.† Assays for circulating endogenous corticotropin were performed on the blood of eight patients, using the adrenal ascorbic acid depletion method of Sydnor and Sayers.[16]

RESULTS

In Table 1 are shown the data concerning initial values obtained in patients with Sydenham's chorea for three of the nonspecific acute-phase reactants: mucoproteins, hexosamines, and nonglucosamine polysaccharides. Although the majority of the values obtained for the mucoproteins in these patients fell within the normal range, the mean value for the entire group was increased significantly over that for normal children (3.4 ± 0.24 mg. per 100 cc. *vs.* 2.5 ± 0.06 mg. per 100 cc. [$p < 0.01$]).

Serum hexosamines were elevated in 8 of 20 patients studied, and the mean value for

Technical assistance was given by Doris F. Tippit, Mary C. O'Brien, and H. Beth Dowding.

Part of this work was done during the tenure of an American Heart Association Research Fellowship (Dr. Done).

From the Lockhart Memorial Laboratory, Department of Pediatrics, University of Utah School of Medicine, and the State Rheumatic Fever Clinics of the Utah State Department of Health.

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* References 4 and 5.

† References 14 and 15.

TABLE 1.—*Acute-Phase Reactants in Chorea*

	N	M	S. E. M.	P
Mucoproteins				
Normal.....	75	2.5	±0.06	....
Chorea.....	25	3.4	±0.24	<0.01
Hexosamines				
Normal.....	37	54	±1.8	....
Chorea.....	20	76	±3.1	<0.01
Nonglucosamine polysaccharides				
Normal.....	71	114	±3.2	....
Chorea.....	22	148	±6.2	<0.01

the entire group was 76±3.1 mg. per 100 cc. Again the difference from the normal mean value of 54±1.8 mg. per 100 cc. is highly significant ($p<0.01$).

The serum nonglucosamine polysaccharides were found to be elevated more consistently than either the mucoproteins or the hexosamines. The mean of 148±6.2 mg. per 100 cc. in the chorea group not only is significantly greater than the mean of 114±3.2 mg. per 100 cc. in the normal group, but exceeds the upper limit of the normal range.

The values observed for each of the acute-phase reactants were analyzed in relation to elevation or nonelevation of the sedimentation rate. The upper limit of normal of the sedimentation rate was considered to be 20 mm/hr.[17] Mean elevations in the concentrations of these acute-phase reactants were found in the presence both of normal and of elevated sedimentation rates.

Table 2 summarizes the data on the plasma 17-hydroxycorticosteroid concentrations. In 40 normal children the range was from 0-28γ per 100 cc., with a mean value of 12.0±1.29γ per 100 cc. In the 28 determinations performed on plasma samples obtained from 23 patients with chorea, the range was from 0-12.8γ per 100 cc., with a mean value of 5.8±0.84γ per 100 cc. The statistical difference between these mean values is highly significant, p being <0.01. It is interesting that the highest value observed in this series (12.8γ per 100 cc.) was no higher than the normal mean value.

TABLE 2.—*Plasma 17-Hydroxycorticosteroid Levels (γ per 100 Cc.) in Untreated Chorea*

	No.	Range	Mean	S. E. M.	P
Normal.....	40	0-28	12.0	±1.29	10·0>
Chorea.....	28	0-12.8	5.8	±0.84	

Bioassays for circulating endogenous corticotropin were performed on the blood of eight of the patients in this series. The results of these assays are presented in Table 3. On each day that an unknown was assayed, the adrenal ascorbic acid depletion that resulted in the test rats was compared with that elicited by standard corticotropin of known potency. For the sake of simplicity, the results were expressed in terms of approximate corticotropin concentrations. These concentrations are expressed as 0, 2.5, 5, and 10 milliunits of corticotropin per liter, which correspond to the doses of standard corticotropin employed. No attempt was made to interpolate between these standard reference points. From Table 3 it can be seen that the level of circulating corticotropin in normal subjects is not high enough to be detected by this technique. Two of the eight chorea patients had no measurable concentration of circulating corticotropin; three had a level of 5.0, and three of 2.5 milliunits (mu)/liter.

TABLE 3.—*Circulating Corticotropin Concentrations in Chorea*

	Cases	Approximate Corticotropin Concentrations, Mu/L.*
Normal.....	12	0†
Chorea.....	B. F.	0.0
	C. E.	5.0
	L. H.	5.0
	A. W.	0.0
	D. J.	2.5
	M. L.	5.0
	C. E.	2.5
	P. A.	2.5

* Milliunits per liter.
† No detectable corticotropin in the blood of 12 normal persons.

TABLE 4.—*Plasma 17-Hydroxycorticosteroid Response to Twenty-Five International Units Corticotropin in Patients with Chorea*

	N	Mean Change,* γ/100 Cc.	S. E. M.	P
Normal.....	40	17.8	1.76	....
Chorea.....	9	20.7	5.13	>0.05

* The values in this column represent the mean increases in plasma 17-hydroxycorticosteroid concentration two hours following the intramuscular injection of 25 I. U. lyophylized corticotropin.

These latter represent abnormally high concentrations of endogenous corticotropin.

Low values of 17-hydroxycorticosteroid concentrations in the presence of simultaneously elevated corticotropin concentrations were found in patients with chorea with or without exudative manifestations of rheumatic fever or elevation of the erythrocyte sedimentation rate. These findings indicate that the adrenals of these persons do not produce enough steroids to maintain normal plasma concentrations in response to greater than normal stimulation by endogenous corticotropin. Despite this evidence of adrenal unresponsiveness, the response to relatively large doses of exogenous corticotropin is normal. As shown in Table 4, in response to the intramuscular administration of 25 I. U. of corticotropin, the mean increase in the concentration of the 17-hydroxycorticosteroids (17-OHCS) in two hours was $20.7 \pm 5.13\gamma$ per 100 cc., as compared to the mean change of $17.8 \pm 1.76\gamma$ per 100 cc. in the normal group.

COMMENT

It has been a common observation that patients with Sydenham's chorea uncomplicated by the exudative manifestations of rheumatic fever need not have an elevation in the sedimentation rate. Likewise, it has been demonstrated that the hyaluronidase inhibitor levels of serum are not elevated in this condition.[18] In the present series, slight but significant elevation in the mean concentrations of serum mucoproteins and hexosamines were observed. Although the majority of the individual values obtained fell within the normal range, a few were definitely elevated, and most of those within the normal range were near the upper limit of that range.

In an earlier study,[7] elevations in the nonglucosamine polysaccharides were found in patients with Sydenham's chorea. This has been observed again in the present series. In contrast to the occasional elevations of mucoproteins and hexosamines observed, the nonglucosamine polysaccharides were found to be quite consistently elevated beyond the normal range. The mean value in this group not only is significantly greater than the mean of the normal group, but exceeds the upper limit of the normal range.

Nonspecific elevations in the concentrations of the serum acute-phase reactants have been demonstrated in a wide variety of diseases.[7] An adrenal mechanism functioning in the control of the serum levels of nonspecific hyaluronidase inhibitor and mucoprotein has been demonstrated.[19] Similarly, these alterations observed in the acute phase reactants in Sydenham's chorea may reflect alterations in adrenal cortex function.

That such an alteration in adrenal cortex function may exist in Sydenham's chorea is well supported by the observations concerning circulating concentrations of pituitary and adrenal hormones. Almost all the patients studied in this series had abnormally low levels of circulating 17-OHCS in randomly selected samples obtained during the course of their disease. In addition several of these same patients had simultaneously elevated levels of endogenous corticotropin. These findings of simultaneously increased levels of corticotropin and decreased circulating levels of 17-OHCS are interpreted as indicating a state of relative adrenocortical insufficiency in chorea patients, such as has been demonstrated previously in patients with rheumatic fever.‡ That this state of adrenal insufficiency is relative and not absolute is demonstrated by the adequate increase in plasma 17-OHCS concentrations in response to the administration of corticotropin. The amount of corticotropin administered in this response test is considerably greater than the total amount of circulating endogenous corticotropin found in these patients.

This state of relative adrenal insufficiency has been demonstrated in patients with acute rheumatic fever after their illness has become well established and in patients in whom the disease is considered inactive.[8] This altered state of adrenal cortex function is present in these patients whether or not there are exudative manifestations of the disease; it is also

‡ References 8 and 9.

present in patients with Sydenham's chorea whether or not there is elevation of the erythrocyte sedimentation rate. In view of the present observations, the validity of classifying chorea as being of psychogenic origin on the basis of a normal erythrocyte sedimentation rate [22] is open to question. In addition, the demonstration of this state of adrenal cortex dysfunction in patients both with rheumatic fever and with Sydenham's chorea indicates another common pathophysiologic abnormality in these two conditions and lends support to the contention that there is an intimate relationship between the two.

It is not known whether this state of adrenal insufficiency bears causal relationship to the onset of chorea, is a result of that disease, or is merely an incidental finding in patients with chorea. In the present state of investigation, there is no definitive understanding of the pathogenesis of this state of relative adrenal cortex insufficiency. In a previous report,[9] three hypotheses were advanced: 1. The adrenal cortex does not or cannot produce its hormones as rapidly or in as great a quantity as in the normal person. 2. The low level of plasma 17-OHCS may reflect an increased rate of tissue utilization or destruction of these hormones. 3. Some adrenal hormone other than 17-hydroxycorticosterone may be present in the blood of these patients in sufficient concentrations to usurp the role of the latter in regulating pituitary release of corticotropin. A fourth possibility that this state of adrenal insufficiency is due to primary pituitary insufficiency seems unlikely in view of the elevated circulating corticotropin levels demonstrated in these patients. Regardless of the mechanism producing this relative adrenal cortex insufficiency, the equilibrium state with regard to the 17-OHCS level indicates that the adrenal cortex is not producing these steroids rapidly enough to maintain a normal concentration in the blood.

It is well known that patients with adrenal insufficiency are much more susceptible to environmental stresses, both physical and psychic. Should a state of relative adrenal insufficiency exist prior to the onset of any one of the manifestations of rheumatic fever, it would seem possible that this would have a deleterious effect on the person's resistance to stress. Thus, a stress, whether it be a severe emotional trauma or a streptococcal infection, in such patients may precipitate an episode of rheumatic fever in the form of polyarthritis, carditis, or in the form of Sydenham's chorea. Just why the disease should take one form in preference to another is not explainable on the basis of present data, except perhaps by the concept of varying end-organ susceptibility.

SUMMARY

In a study of 30 patients with Sydenham's chorea, significant elevations in the mean concentrations of serum mucoproteins, hexosamines, and nonglucosamine polysaccharides were observed.

Abnormally low concentrations of plasma 17-hydroxycorticosteroids were found in these patients in association with elevated levels of circulating endogenous corticotropin.

These findings were interpreted as indicating a state of relative adrenal insufficiency. That this state of adrenal insufficiency was relative and not absolute was shown by the normal response of the plasma 17-hydroxycorticosteroids to relatively large test doses of corticotropin.

The significance of these findings is discussed.

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Sydenham's Chorea

II. Effects of Hormone Therapy

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Evidence suggesting the existence of a state of relative adrenal insufficiency in patients with Sydenham's chorea has been presented.[1] Similarly, a state of relative adrenal insufficiency has been shown to exist in patients with active or inactive rheumatic fever.* Since corticotropin and cortisone have been reported to be efficacious in therapy of exudative rheumatic fever,† and since similar biochemical and physiological abnormalities occur in patients with both of these diseases, it seems logical that hormone therapy might be of value in chorea.

In the past four years several case reports on the use of corticotropin and cortisone in the treatment of Sydenham's chorea have appeared in the literature.‡ Results reported by these investigators have been widely divergent, some reporting favorably on hormone therapy, whereas others report that this form of therapy does not alter the clinical course of the disease. The purpose of this communication is to report the results of hormone therapy in 13 attacks of Sydenham's chorea in 11 patients.

MATERIALS AND METHODS

The patients included in this study were six boys and five girls, ranging in age from 4½ to 14 years. Two of the patients had recurrences of their chorea, which were treated with a second course of hormone therapy. Patients were selected for hormone therapy only if they manifested severe incapacitating chorea and if no definite improvement occurred spontaneously during a preliminary observation period (2 to 20 days) after admission to the hospital.

Prior to and throughout the course of therapy these patients were subjected to frequent clinical and laboratory evaluation by the methods previously described.§ All patients were submitted to cardiac fluoroscopy and roentgenologic examination before institution of therapy and as often thereafter as seemed indicated clinically. Electrocardiograms, including the unipolar leads, were taken before and at frequent intervals during therapy.

Hormone therapy was initiated in these patients in accordance with the regimen previously suggested as optimal in the management of acute rheumatic fever.[14] Nine patients received lyophylized corticotropin‖ intramuscularly. The daily dose (0.9-2.0 I. U. per lb/day) was administered in four equal portions given at six-hour intervals.

All patients were maintained on bed rest. In addition to hormone therapy, each, with the exception of one, received large daily supplemental doses of ascorbic acid and daily penicillin prophylaxis. In all patients the initial daily dose of corticotropin was maintained until it appeared that maximum clinical improvement had been obtained. The dose then was tapered gradually over a period of several days to a few weeks; in no case was the drug withdrawn abruptly.

Two patients were treated with corticotropin-gel,¶ which was administered intramuscularly twice daily in intial doses of 1.0 and 2.4 I. U. per lb/day. Two

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* References 2 and 3.

† References 4-14.

‡ References 15-21.

§ References 1 and 14.

‖ Acthar: Furnished by The Armour Laboratories, Chicago.

¶ Acthar-Gel: Furnished by the Armour Laboratories, Chicago.

patients received cortisone # intramuscularly for two days and then orally in initial daily doses of 3.3 and 5.4 mg/lb/day, doses now considered to be larger than necessary.

OBSERVATIONS

Case Reports

Case 1.—E. N., 9-year-old white boy, admitted April 10, 1951. Previous attack: one, 1949. Family history negative for rheumatic fever.

Present Illness.—One month prior to admission the patient had a sore throat with fever, which responded to prompt treatment with penicillin. A week later he became listless and tired and had minor epitaxes. Examination at that time revealed low-grade fever, elevated E. S. R., and accentuation of a previously existing heart murmur. There was little improvement on bed rest, and six days prior to admission the patient's mother noted choreiform movements which became progressively more severe during the next two days.

Physical Examination.—Physical examination revealed uncontrollable purposeless movements of the extremities, marked facial grimacing, and gross incoordination. There was a Grade 2 systolic murmur, maximum in the third intercostal space along the left sternal border.

Laboratory Findings.—E. S. R., 42 mm/hr.; WBC, 15,150 (77% P. M. N.); electrocardiogram, prolonged P-R interval and delay in activation of the right ventricle.

Hospital Course.—On admission the patient's choreiform movements were so violent as to require side-boards on his bed, despite sedation with phenobarbital (64 mg. t. i. d.). After four days of observation during which no change in choreiform activity was noted, the patient was treated with lyophilized corticotropin, 25 I. U., q. 6 h. intramuscularly, and ascorbic acid, 250 mg. b. i. d. There followed a seemingly dramatic improvement, and on the seventh day choreiform activity was minimal, although the patient still had considerable difficulty with movements requiring finer coordination, such as writing. There was a concomitant improvement in his cardiac status as shown by a return of his ECG to normal.

Case 2.—D. I., 4-year-old white boy, admitted July 18, 1951. No previous chorea or rheumatic fever. Family history negative for rheumatic fever at time of admission. (See J. I., Case 3.)

Present Illness.—When the patient began to walk, at the age of 14 months, it was noted that he dragged his left leg and foot. Aside from this difficulty, he remained in general good health until four months prior to admission, at which time he developed typical grand-mal seizures, seven such seizures occurring during the next two months. Nine days prior to admission he developed a staggering gait with frequent falling. In addition he had continuous involuntary purposeless movements and twitching of his extremities. Four days prior to admission he developed clumsiness of speech and lost control of his eye movements.

Physical Examination.—Physical examination revealed an extremely ataxic gait, and constant purposeless movements of the extremities. Speech was indistinct, with clicking and stuttering. Deep tendon reflexes were hypoactive; no pathological reflexes were elicited.

Laboratory Findings.—E. S. R., 35 mm/hr.; WBC, 16,800, with a slight P. M. N. preponderance; antistreptolysin titer, 200 Todd units. ECG revealed a prolonged P-R interval.

Hospital Course.—During the first three weeks choreiform activity became progressively worse, and despite heavy phenobarbital sedation (64 mg. t. i. d.), it was necessary to pad the patient's bed to prevent injury. Then cortisone therapy was started (50 mg. q. i. d. for two days and then 25 mg. q. i. d.). There was almost immediate improvement in the patient's clinical state, but ECG evidence of carditis persisted. The patient had several grand-mal seizures during his hospital stay; none, however, occurred while he was receiving full doses of cortisone. Eventually these were controlled adequately by the administration of diphenylhydantoin (Dilantin) (0.1 gm. b. i. d.) and phenobarbital (64 mg. h. s.). At the time hormone therapy was discontinued the patient had no evidence of rheumatic activity except a prolongation of the P-R interval. Although this patient has not had adequate follow-up, he was seen once soon after discharge, at which time the P-R interval had returned to normal.

Case 3.—J. I., 6½-year-old girl (sibling of D. I., Case 2), admitted July 30, 1951. No previous chorea or rheumatic fever. The patient's home environment was not wholesome. The mother had remarried, but in both marriages there was much discord. Considerable violence had been expressed between the parents and toward the patients D. I. and J. I.; both children were quite fearful of their stepfather.

Present Illness.—The patient was in apparent good health until 10 days prior to admission, the day of admission of her sibling, when she became anorexic, developed lability of mood and clumsiness of speech, and became clumsy in her movements. Five days later she developed gross purposeless movements of the upper and lower extremities, which became progresively worse until the time of admission.

Physical Examination.—Physical examination revealed gross purposeless movements of the extremities, facial grimacing, and mood lability. Cardiac

Cortone: Supplied by Merck & Company, Inc., Rahway, N. J.

auscultation revealed a Grade 1 basilar systolic murmur and a prominent split pulmonic second sound.

Laboratory Findings.—E. S. R., 30 mm/hr.; WBC, 4,800; ECG and cardiac fluoroscopy, normal.

Hospital Course.—During the first two weeks, despite heavy phenobarbital sedation (65 mg. t. i. d.), choreiform activity was so marked as to necessitate padding the patient's bed for protection. During this time the patient developed prolongation of the P-R interval and right ventricular conduction delay on serial ECG's. Cortisone therapy was begun (50 mg. q. 6. h.). Dramatic clinical improvement was noted by the 3d day of therapy, and by the 15th day all evidences of choreiform activity had disappeared. Tapering of dose was begun on the 20th day, and cortisone was discontinued on the 42d day. At the time of discharge, on Oct. 21, 1951, there was no evidence of chorea, and no murmurs were heard. P-R interval was still at the upper limits of normal.

CASE 4.—M. H., 12-year-old white girl, admitted Feb. 8, 1952. Two previous episodes of chorea.

Present Illness.—Two weeks prior to admission the patient complained of easy fatigability and emotional lability; speech became rapid and indistinct, and she developed uncontrollable purposeless movements of her extremities.

Physical Examination.—Physical examination revealed rapid clicking speech, clumsy gait, and gross involuntary purposeless movements. Behavior was silly and inappropriate. There was a Grade 2 apical systolic murmur transmitted along the left sternal border and into the axilla.

Laboratory Findings.—E. S. R., 19 mm/hr.; WBC and differential, within normal limits; ECG and chest fluoroscopy, normal.

Hospital Course.—During her first two days in the hospital, the patient's chorea became somewhat less severe, although she received no sedation. However, severe activity remained, and corticotropin therapy was begun (25 I. U. q. 6. h.). Under therapy the patient gradually improved, and by the 16th day choreiform movements were minimal. On the 18th day no evidence of chorea could be elicited. From the 14th day the dose of corticotropin was tapered gradually until the drug was discontinued on the 21st day, the day of discharge. At no time did she develop any signs or symptoms of active carditis, and follow-up examinations revealed no change in cardiac status.

CASE 5.—W. D., 6-year-old white boy, admitted Jan. 15, 1952. One previous attack. Family history for rheumatic fever negative.

Present Illness.—In May, 1951, the patient had been hospitalized briefly for acute abdominal pain but was discharged without surgery, and a diagnosis of acute mesenteric lymphadenitis was made. In June, 1951, he had Sydenham's chorea, with general lability of mood, quick movements of the shoulders and trunk, and difficulty in manual and lingual coordination. Little improvement occurred until December, 1951, when he had severe rubeola. At this time there was a definite cessation of choreiform activity. Following this illness, the patient had a daily low-grade fever. In addition he had transient "reddish circular areas" appearing on the skin of the forehead and back of the neck. Choreiform movements reappeared.

Physical Examination.—Physical examination revealed gross tremor of the hands, with jerking of the wrists, arms, and shoulders. Speech was explosive and clumsy. There was a soft systolic murmur over the region of the apex, variable with head position and posture. P_2 was loud.

Laboratory Findings.—E. S. R., 37 mm/hr.; WBC, 12,600, with a P. M. N. predominance. ECG, although not definitely abnormal, showed some flattening of the T-waves when compared to a previous tracing. Fluoroscopy revealed slight atrial enlargement.

Hospital Course.—Corticotropin therapy (20 I. U. q. 6. h.) was begun on the third hospital day. Within a week there was definite clinical improvement, and by the 16th day all clinical evidence of chorea had disappeared. From the 23d day the corticotropin dose was gradually tapered, and the drug was discontinued on the 29th day of therapy. The patient appeared to be clinically well. Fluoroscopy and ECG were normal. There has been no recurrence.

CASE 6.—B. P., 14 year-old white boy, admitted June 13, 1952. Strong family history of rheumatic fever.

Present Illness.—At the age of 4 years the patient had an attack of rheumatic fever. At the age of 9 years he had his first episode of Sydenham's chorea, for which he was hospitalized and treated by fever therapy with little improvement. Several months were required for cessation of all choreiform activity, and thereafter followed a long history of easy fatigability, myalgia, and arthralgia. Nine months before admission the patient sustained a severe head injury. This incident was followed by a recurrence of his chorea, which became so severe as to necessitate hospitalization in another institution in March, 1952. There he was given a three-week trial of corticotropin therapy, with considerable clinical improvement, but without cessation of all choreiform activity. Following this he was placed in a convalescent home, and his chorea became progressively more violent until he was referred to this hospital.

Physical Examination.—Physical examination revealed uncontrollable purposeless movements of the extremities. There were extraneous jerking movements of the eyes. Speech was hesitant, halting, and somewhat indistinct. There was a soft systolic mur-

mur loudest in the second left interspace along the sternal border.

Laboratory Findings.—E. S. R., 4 mm/hr.; WBC, normal; ECG and fluoroscopy, normal.

Hospital Course.—During the first 10 days his chorea progressed in severity until it was necessary to pad his bed to protect him from bodily harm. On the 10th day, therapy with corticotropin (37.5 I. U. q. 6. h.) was begun. Within three days there occurred dramatic improvement. From the 17th day of therapy corticotropin dose was tapered gradually until the drug was discontinued on the 48th day. The patient was discharged on the 55th day with only minimal choreiform movements.

He has remained clinically well. Follow-up examination 18 months after discharge reveals no detectable evidence of cardiac damage or choreiform activity.

CASE 7.—C. E., 10-year-old white girl, admitted July 2, 1952. No previous chorea or rheumatic fever. No family history of rheumatic fever.

Present Illness.—Three weeks prior to admission, she had a sore throat which was not treated. Following this she became increasingly irritable and developed involuntary purposeless movements, which became progressively more severe until she was unable to feed herself.

Physical Examination.—Physical examination revealed an irritable thin pale girl unable to sit quietly. There were constant purposeless movements of the extremities, facial grimacing, and indistinct speech. Cardiac findings were normal.

Laboratory Findings.—E. S. R., 33 mm/hr.; WBC and differential, normal; ECG and cardiac fluoroscopy, normal. EEG was grossly abnormal, with slow frequencies and rare sharp discharges.

Hospital Course.—Despite phenobarbital sedation, she failed to improve, and after a two-week observation period, corticotropin therapy (37.5 I. U. q. 6. h.) was begun. Within a day, the patient again was able to feed herself. From that time gradual but definite improvement was noted. An EEG taken on the 10th day of therapy showed definite improvement. Thereafter no further change occurred. From the 31st day of therapy the corticotropin dose was tapered gradually until the drug was discontinued on the 43d day. There was no increase in the minimal choreiform activity still present, and the patient was discharged to be followed in the outpatient clinic.

CASE 7 (Second Admission, July 20, 1953).—*Present Illness.*—The patient was followed regularly in the outpatient clinic. From time to time she showed slight choreiform activity. Prophylactic penicillin was taken only irregularly. Ten months after discharge the patient had a tooth extracted. One week later she again developed frank chorea and was admitted.

Physical Examination.—Physical examination revealed choreiform movements of her extremities, her gait being clumsy. Speech was rapid and indistinct. Hand grip showed marked fluctuation bilaterally. Cardiac findings again were normal.

Laboratory Findings.—E. S. R., 15 mm/hr.; WBC, normal. ECG, fluoroscopy, and EEG showed no change from previous examinations.

Hospital Course.—One week after admission, therapy with corticotropin-gel (40 I. U. b. i. d.) was begun. Some immediate improvement was noted, and two weeks later chorieform activity was minimal. On the 12th day of therapy tapering of the drug was started, and the drug was discontinued on the 18th day. On discharge five days later she still had minimal chorea. On follow-up two weeks later there was no detectable choreiform activity.

CASE 8.—L. M., 13-year-old white girl, admitted April 24, 1952. No previous chorea or rheumatic fever. Family history negative for rheumatic fever.

Present Illness.—Three weeks prior to admission the patient became clumsy and developed involuntary purposeless movements of her right arm. She chewed her tongue and was unable to feed herself. Speech was indistinct and gait clumsy.

Physical Examination.—Physical examination revealed constant purposeless movements of the head and arms, hyperactive reflexes, and pendular knee jerks. Speech was rapid, clipped, and indistinct. The patient was unable to walk. There was a loud split P_2 and a Grade 2 systolic murmur.

Laboratory Findings.—E. S. R., 29 mm/hr.; WBC, 11,600, with a normal differential. Fluoroscopy and ECG, normal. EEG showed abnormal discharges in the posterior quadrants, most prominent in the right occipital area.

Hospital Course.—It was necessary to pad the patient's bed, since choreiform activity was uncontrolled by heavy phenobarbital sedation. On the fourth hospital day therapy with corticotropin (37.5 I. U., q. 6 h.) was started. Within four days marked improvement occurred, and within seven days it was possible to discontinue phenobarbital sedation. Within three weeks only minimal choreiform activity remained. From the 62d day of therapy the dose of corticotropin was tapered gradually until the drug was discontinued on the 72d day of therapy. Minimal chorea was still present at the time of discharge on July 9, 1952.

CASE 8 (Second Admission Sept. 6, 1952).—Minimal chorea persisted after discharge. One month later, with the onset of menstruation, she again developed gross involuntary movements of her extermities, indistinct speech, and clumsy gait. These symptoms persisted until admission three weeks later.

Physical Examination.—Physical examination revealed constant involuntary movements of her fingers and toes and random movements of her arms. Speech was rapid and halting, with clicking of the tongue. Cardiac auscultation revealed a reduplicated P_2.

Laboratory Findings.—E. S. R., 18 mm/hr.; WBC, normal; ECG was within normal limits. Repeat EEG revealed no change.

Hospital Course.—Nine days after admission, corticotropin therapy (37.5 I. U. q. 6 h.) was started again. Improvement was prompt, and within two weeks only mild chorea persisted. From the 32d day of therapy the corticotropin dose was gradually tapered until the drug was discontinued on the 80th day. The patient was discharged fully ambulatory and asymptomatic.

CASE 9.—L. H., 12-year-old white boy, admitted Sept. 20, 1952. Episode of rheumatic fever and chorea, age 7 years. Hospitalized for continuous choreiform activity, 1949-1951. No family history of rheumatic fever.

Present Illness.—One year prior to this admission the patient had spent four months in this hospital for the treatment of chorea. Because of his unwholesome background a diagnosis of psychogenic chorea had been made, and the patient was treated by extensive psychotherapy. On discharge from the hospital he was placed in a foster home. The patient remained well, and psychotherapy was continued in the Child Guidance Clinic. During his summer vacation, nine months after discharge, he returned home. He was unable to adjust himself to the family situation and to the competition of his siblings. Approximately a month prior to admission he became hyperexcitable and developed involuntary twitching and his speech became indistinct and explosive. The day prior to admission he developed marked purposeless movements of the extremities and an uneven staggering gait; on the day of admission he complained of blurring of vision.

Physical Examination.—Physical examination revealed constant choreiform movements of the extremities and facial grimacing. Speech was slurred and explosive. There was a Grade 2 apical systolic murmur transmitted to the axilla. There were generalized hyporeflexia and pendular knee and ankle jerks.

Laboratory Findings.—E. S. R., 8 mm/hr.; WBC, normal; fluoroscopy and ECG, normal. EEG was diffusely abnormal.

Hospital Course.—A trial of inhospital psychotherapy and phenobarbital sedation was given during the first two and one-half weeks of hospitalization. No improvement was noted in the patient's condition; his activity seemed to increase. On the 20th hospital day therapy with corticotropin (37.5 I. U. q. 6 h.) was started. Within a week considerable improvement was noted. From the 35th day the corticotropin dose was gradually tapered until the drug was discontinued on the 57th day. Minimal choreiform movements remained. On Jan. 11, 1953, the patient was discharged to a foster home, where he remained only a short while before returning to his own home. Since then he has been well, and all evidence of chorea has disappeared. His murmur progressively decreased in intensity; it has not been audible since six months after discharge.

CASE 10.—P. A., 14-year-old Mexican boy, admitted Aug. 3, 1952. One previous attack of rheumatic fever and chorea. Family history negative for rheumatic fever.

Present Illness.—Six weeks prior to admission the patient developed fatigability and anorexia. Two weeks later this was followed by the appearance of an involuntary coarse tremor of the right arm. Involuntary purposeless movements of his right leg, difficulty in chewing, and indistinct speech developed during the next 10 days. He also experienced a loss of memory for recent events, but retained a normal memory for remote events.

Physical Examination.—Physical examination revealed gross involuntary movements, predominately of the right side. Speech was jerking, hesitant, and slightly slurred. The tongue protruded to the right, and there was questionable fasciculation. The grip of the right hand was extremely weak, and slow "milking movements" were felt when the patient grasped the examiner's hand. There were no murmurs.

Laboratory Findings.—E. S. R., 25 mm/hr.; WBC, normal. Fluoroscopy, normal. ECG showed an incomplete right bundle-branch block.

Hospital Course.—One week after admission, therapy with corticotropin-gel (50 I. U. b. i. d.) was begun. Inadvertently, no ascorbic acid was given. No response to this regimen was observed. On the 11th day of therapy the dose was increased to 75 I. U. b. i. d. Still no response was obtained. On the 26th day the dose was gradually tapered until the drug was discontinued on the 31st day. As the dose was being tapered some improvement was noted in his chorea, but on discharge the patient still had moderate activity. Repeat ECG revealed no change. Other cardiac findings remained normal.

CASE 11.—K. S., 8-year-old white girl, admitted March 5, 1952. Family history negative for rheumatic fever.

Present Illness.—Three years prior to admission the patient had an episode of severe abdominal pain associated with a high fever. She was hospitalized a few days and then discharged, no diagnosis having been made. After this she occasionally complained of arthralgia. Two years prior to admission heart murmurs were noted, but these were not considered

to be of any significance. For a year prior to admission she had episodes of epistaxis occurring once or twice a week. Three months before admission the patient developed fever and complained of severe pain in her wrists, elbows, knees, and neck, but no frank arthritis occurred. Simultaneously she developed considerable emotional lability, nervousness, clumsiness of gait, and impaired manual and lingual dexterity.

Physical Examination.—Physical examination revealed jerking movements of the extremities and indistinct explosive speech. The P. M. I. was diffuse in the fifth left intercostal space in the anterior axillary line. A systolic thrill was palpable over the cardiac apex. The rate was rapid (142). A Grade 4 systolic murmur was heard over the apex and was transmitted along the left sternal border and into the axilla. P_2 was loud.

Laboratory Findings.—E. S. R., 29 mm/hr. (two days later, 42 mm/hr.); WBC, normal; fluoroscopy and x-ray revealed the heart size to be at the upper limits of normal as measured by the cardiothoracic ratio. Definite atrial enlargement and slight left ventricular enlargement were present.

Hospital Course.—On the third hospital day therapy with corticotropin (20 I. U. q. 6 h.) was begun. The E. S. R. returned to normal in seven days. Simultaneously there was a disappearance of fever and a marked diminution in choreiform movements. From the 14th day of therapy the corticotropin dose was gradually tapered until the drug was discontinued on the 23d day. The patient was discharged on April 2, 1952, with no evidence of chorea. Cardiac findings remained unchanged. On subsequent examinations the cardiac murmur became less intensive until it was no longer audible on her last visit, January, 1953.

In Table 1 are summarized the clinical features of the above patients. Of the 13 attacks of chorea, 5 were initial attacks and 8 represented recurrences. Four patients had a definite and one a questionable past history of rheumatic fever in which the major manifestation was arthritis and/or carditis. Six patients had clinical, electrocardiographic, or fluoroscopic evidence of carditis. In each of these patients the E. S. R. was elevated during the pretherapy period and during the early period of therapy. In only one patient (L. M.), in whom no evidence of carditis was present, was the E. S. R. elevated; this patient was menstruating.

In Table 2 are summarized the data pertaining to hormone therapy in these patients and the results of this therapy. The duration of therapy before the initial dose of hormone was tapered ranged from 12 to 64 days, and the total duration of therapy ranged from 18 to 80 days. In most of the cases initial improvement occurred within the first week of therapy. In five patients the response noted was classified as "dramatic." Two of these patients, D. I. and J. I., before therapy had severe encephalitic symptomatology. Both were stuporous and had such violent choreiform activity that they required a padded crib to prevent bodily harm. Within three days after the beginning of cortisone therapy, both were able to walk, talk, and feed themselves. Patient B. P. before therapy had such violent choreiform movements that he was thrown from his bed several times. Within three days after therapy with corticotropin had been initiated, only minimal choreiform movements remained. C. E., who initially was unable to feed herself, was able to do so the day following the initiation of corticotropin therapy. L. M. before therapy had such violent chorea that despite heavy phenobarbital sedation and quiet surroundings she required bed padding and restraints to prevent bodily harm. Speech was incomprehensible. Within four days after therapy with corticotropin was begun, the patient showed marked improvement, no longer requiring these precautions. Speech became comprehensible, and the patient was able to feed herself. In all with the exception of one patient marked improvement occurred within three days after the initiation of therapy. Only one patient in this series failed to show definite response to therapy.

At the time of discharge from the hospital only four patients had shown complete cessation of all choreiform activity. With the exception of the patient who failed to respond to therapy, all the rest had minimal residual choreiform movements elicitable only on fine clinical testing. In all but one patient with carditis there occurred definite clinical and electrocardiographic improvement during therapy. In this patient (D. I.), the P-R interval which had been prolonged throughout therapy, had returned to normal by the time of the first and only clinic visit.

TABLE 1.—*Hormone Therapy of Chorea*

Patient	Therapy: Drug	Therapy: Initial Dose	Therapy: Duration of Therapy: Initial	Therapy: Duration of Therapy: Total	Initial Improvement: Days	Initial Improvement: Degree	Chorea on Discharge	Cardiac Status: Initial	Cardiac Status: Discharge
E. N.	Corticotropin	1.7 I.U./lb./day	15	30	6	Marked	Minimal	Changing M.I.* murmur; prolonged P-R	P-R normal; M.I. less intense
D. I.	Cortisone	3.3 mg./lb./day	40	47	3	Dramatic	None	Prolonged P-R; no murmurs	P-R still prolonged no murmur
J. I.	Cortisone	5.4 mg./lb./day	20	42	3	Dramatic	None	Prolonged P-R; no murmur	P-R upper limits; normal
M. H.	Corticotropin	0.9 I.U./lb./day	14	21	16	Marked	Minimal	Normal	Normal
W. D.	Corticotropin	2 mg./lb./day	23	29	7	Marked	None	Variable murmur; P_2 incr.; T wave change ECG	No murmur; normal ECG
B. P.	Corticotropin	1.3 I.U./lb./day	17	55	3	Dramatic	Minimal	Normal	Normal
C. E. 1st Adm.	Corticotropin	2 I.U./lb./day	31	43	1	Dramatic	Minimal	Normal	Normal
C. E. 2d Adm.	Corticotropin-gel	1 I.U./lb./day	12	18	3	Marked	Minimal	Normal	Normal
L. M. 1st Adm.	Corticotropin	1.5 I.U./lb./day	64	72	4	Dramatic	Minimal	Changing murmur	Normal
L. M. 2d Adm.	Corticotropin	1.9 I.U./lb./day	32	80	3	Marked	Minimal	Normal	Normal
L. H.	Corticotropin	2 I.U./lb./day	35	57	3	Marked	Minimal	Murmur of M.I.*	Murmur disappears
P. A.	Corticotropin-gel	2 I.U./lb./day	15	31	..	Slight	Moderate	RBBB †	RBBB †
K. S.	Corticotropin	1.6 I.U./lb./day	14	23	3	Marked	None	M.I.* Grade IV	Murmur decreased

* M.I. indicates murmur of mitral insufficiency.
† Right bundle-branch block.

TABLE 2.—*Clinical Features of Cases Selected for Hormone Therapy*

Patient	Age, Yr.	Sex	Previous Chorea	Previous Arthritis Carditis	Possible Precipitating Factor	Severity of Chorea	E. S. R.	Clinical Evidence of Carditis
E. N.	9	M	1	?	? Strep sore throat	Severe	Elev.	Yes
D. I.	4½	M	0	None	Onset of grand-mal epilepsy	Severe	Elev.	Yes
J. I.	6	F	0	None	Hospitalization of brother	Severe	Elev.	Yes
M. H.	12	F	2	Hip pain; abd. pain	None apparent	Severe	Nor.	No
W. D.	6	M	1	None	Measles with ? strep sore throat	Moder. severe	Elev.	Yes
B. P.	14	M	1	1 attack arthritis carditis	Head injury	Severe	Nor.	No
C. E.	9	F	0	None	Illegitimate pregnancy of mother	Severe	Nor.	No
C. E.	10	F	1	None	Second illegitimate pregnancy of mother; tooth extraction	Severe	Nor.	No
L. M.	12	F	0	None	? Strep sore throat	Severe	Nor.	?
L. M.	12½	F	1	None	None apparent	Severe	Elev.	No
L. H.	12	M	Several	1 attack arthritis; 1 attack carditis	Return to unwholesome competitive home environment	Severe	Nor.	Yes
P. A.	14	M	1	Poly-arthritis; carditis	None apparent	Severe; Hemi-chorea	Nor.	None
K. S.	8	F	0	?	?	Severe	Elev.	Yes

COMMENT

Since its overt manifestations are self-limited, chorea has been considered a benign disease. Recent long-term studies of chorea patients, however, cast doubt on this assumption. The delayed appearance of rheumatic heart disease, especially "pure" mitral stenosis, is not an infrequent occurrence in patients whose only symptomatology had been chorea.[22] In another long-term study, Jacobsen [23] found practically no differences with respect to the degree and nature of residual cardiac damage between a group of patients in whom the initial manifestation of rheumatic fever was chorea and a group in whom it was arthritis or carditis. Also it has been shown that in patients with chorea the risk of a recurrence of this or some other major manifestation of rheumatic fever is somewhat greater than that in patients whose initial symptomatology consisted of arthritis or carditis.[23] In view of these observations it seems that prevalent concepts of chorea as a benign disease must be revised.

Severe psychic stress often has been noted to precede the onset of an attack of chorea. This has been the basis for the concept of the dichotomy of "rheumatic" and "nonrheumatic" chorea and has given impetus to attempts at psychotherapy in the latter. Such a nonspecific test as the sedimentation rate has been proposed as the criterion for differentiating between these two forms of chorea.[24] With the exception of three patients in the present series, a severe physical or psychic stress was present in immediate temporal relation to the onset of the patient's chorea (Table 1). As indicated in the Table, there was little correlation between the nature of the predisposing cause and the presence or absence of concomitant carditis or elevated E. S. R. Furthermore, although there is general agreement that the precipitating factor in most cases of exudative rheumatic fever is a preceding streptococcal infection, cases which apparently were precipitated by a severe psychic or physical stress have been reported not infrequently.[22]

It has been shown that in the early acute phase of rheumatic fever the 17-hydroxycorticosteroid levels of the blood are elevated and that these levels progressively decrease until, after about the third week of the illness, they are lower than normal.* At this time circulating levels of corticotropin are increased, and, therefore, a state of relative adrenal cortex insufficiency exists. It has been observed many times that chorea does not coexist very frequently with acute exudative rheumatic fever and that with the appearance of acute polyarthritis chorea often disappears. Chorea also has been noted to disappear during acute illnesses, such as measles, in which there is considerable stress (patient W.D.). In addition, it has been observed frequently that as the rheumatic fever patient recovers in respect to his exudative manifestations chorea often appears. These clinical observations are in conformity with the steroid patterns observed in patients with rheumatic fever and chorea. Thus, whether the patient develops arthritis or chorea may depend upon the effective functioning level of the pituitary-adrenocortical system during the course of his disease process.

Upon discontinuation of hormone therapy the concentrations of the plasma 17-hydroxycorticosteroids are very low in patients treated with cortisone or corticotropin for either chorea or rheumatic fever.[25] Despite these low concentrations of plasma 17-hydroxycorticosteroids, in no patient did a clinical rebound in the form of a recurrence of the symptomatology of chorea occur. The reason for this, although not clear, might possibly be related to the absence of a precipitating factor. It might also be pointed out that a parallel situation exists in patients with inactive rheumatic fever in whom low levels of 17-hydroxycorticosteroids are present and who do not develop any manifestations of rheumatic activity in the absence of an appropriate precipitating cause.

Therapy in chorea has been directed at control of the symptomatic manifestations rather than correction of the basic pathologic state. Many therapeutic agents have been employed.† Of these, probably phenobarbital

* References 2 and 3.

† References 26-34.

sedation has proved consistently most effective, although in occasional patients, seemingly dramatic results have been associated with other forms of therapy.‡ Because of the common misconception that chorea is a benign disease, many of the precautions observed in the care of other rheumatic fever patients have been omitted in the care of these patients.

Approximately 60% to 70% of all patients having rheumatic fever sooner or later have one or more recurrent attacks, and the risk of recurrence seems somewhat greater in the patient who has had chorea.[23] Therefore, prophylaxis seems as important in the patient with chorea as in the patient with rheumatic fever, and all chorea patients should be placed on either sulfonamide or penicillin prophylaxis, according to the recommendations of the American Heart Association for the prevention of streptococcal infections. All patients in this series received such prophylaxis while in the hospital, and all were discharged on continuous prophylaxis.

Since the pathologic physiology of chorea has not been understood, therapy necessarily has been empirical, usually directed toward suppressing the overt manifestations of the disease. The demonstration that a state of relative adrenal insufficiency exists in patients with this disease permits a more rational basis for therapy. The abnormally low concentrations of circulating 17-hydroxycorticosteroids can be increased either directly by the administration of cortisone or Compound F or indirectly by the administration of corticotropin. That these patients are capable of producing an adequate steroid level in response to corticotropin stimulation indicates that their state of adrenal insufficiency is relative and not absolute.[1]

With the exception of one patient, each also received large daily supplemental doses of ascorbic acid.[14] It was originally suggested that the bettter clinical response to hormone therapy observed in patients given ascorbic acid was dependent upon the need of the adrenal cortex for this compound in order to produce adequate amounts of its steroids. With the demonstration of very high levels of 17-hydroxycorticosteroids in scorbutic guinea pigs which are lowered to near normal levels by the administration of ascorbic acid[35] this rationale became untenable. It now appears that ascorbic acid may function in the peripheral utilization of the 17-hydroxycorticosteroids.§ In this regard it should be noted that the only patient in the series who did not respond satisfactorily to corticotropin therapy was the one who received no ascorbic acid.

The therapy of chorea should have two goals. The immediate goal is the control of the ofttimes violent purposeless movements. The long-term and by far the more important goal is the prevention of cardiac damage. Evidence has been reported recently that hormone therapy appears to be effective in preventing residual cardiac damage in patients with rheumatic carditis.‖ At the present time the number of patients with chorea treated with hormones is too few and the period of follow-up too short to attempt any evaluation of the effect of this therapy on the residual cardiac status. Therefore, the only evaluation that was made at this time was the effect of hormone therapy in the control of the symptomatology of chorea. Satisfactory and often dramatic control of the symptomatology was obtained in all but one of the patients of this series, and in this patient, some improvement did occur.

SUMMARY

The results of 13 courses of hormone therapy in 11 patients with Sydenham's chorea are presented.

In 12 instances a good symptomatic response was obtained. Some of the factors which may have accounted for the one failure of therapy are discussed.

No attempt has been made to evaluate the effects of this therapy on the eventual cardiac status.

‡ References 26-34.

§ Unpublished data.

‖ References 37 and 38.

The importance of antibiotic or chemotherapeutic prophylaxis in patients who have had chorea is emphasized.

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Intravenous Cholecystography with Cholografin in Infants

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This paper reports the use of Cholografin (disodium salt of N,N′-adipyl-bis-[3-amino-2,4,6-triiodo]-benzoic acid) for visualization of the gall bladder in infancy. Cholecystography has been difficult and unsatisfactory in this age group. These preliminary studies are presented because Cholografin appears to be superior to any of the contrast materials previously used for this purpose in the early months of life.

Cholografin is identical with Biligrafin of Schering, A. G., and has been subjected to clinical trials in Germany which were reported in 1953.* Cholografin is a crystalline powder readily soluble to about 20% in water to give a colorless isotonic solution. It has a higher iodine content than other comparable contrast media. Cholografin is given intravenously and is excreted by the liver, the first traces appearing in the bile within a few minutes. The extrahepatic ducts may be visualized in adults within 15 to 20 minutes following injection. Filling of the gall bladder begins at one hour and is maximal at two to two and one-half hours. About 90% of the drug is eliminated in the feces, and 10% or less is excreted by the kidneys. The route of excretion is altered when liver function is impaired; the drug is then largely excreted by the kidneys within the same time period required by the normal liver.

Nausea and occasional vomiting may follow injection of the drug. There is no change in liver function, renal function, blood pressure, or heart rate after injection. Fever, chills, recurrent icterus, and increasing liver damage was seen when Cholografin was administered to patients with jaundice and liver damage.[5]

Püschel[1] used the identical compound Biligrafin in adults and obtained good visualization of the extrahepatic ducts 20 to 60 minutes after injection and excellent cholecystograms at 2 to 3 hours. Berk and coworkers,[6] in Philadelphia, using 40 to 60 cc. of 20% Cholografin in 30 adult patients, reported that of 9 with intact gall bladders, the common duct visualized in 6 and the gall bladder in 7; of 21 with gall bladders removed, the common duct visualized in 19. They noted that the quality and degree of visualization were equal to those of any other contrast material and that there was a good correlation between poor liver function and failure to eliminate the drug. No toxic effects or untoward reactions occurred in either series.

Cholecystograms in infancy are difficult to obtain for the following reasons[7]: (1) immaturity of the infant liver in its ability to excrete the various contrast media; (2) the small size of the gall bladder and its position, well embedded within the liver, especially during the early months of life; (3) the frequency of gas in the bowel obscuring the gall bladder, and (4) greater intestinal mo-

Cholografin (disodium salt of N,N′-adipyl-bis-[3-amino-2,4,6-triiodo]-benzoic acid) was supplied by E. R. Squibb & Sons, Division of the Mathieson Chemical Corporation.

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* References 1-4.

TABLE 1.—*Comparison of Cholecystograms Made with Iodopanoic Acid and Cholografin* *

	Age							
	0-3 Mo.		4-6 Mo.		7-12 Mo.		12-24 Mo.	
	No. Examined	Per Cent Visualized	No. Examined	Per Cent Visualized	No. Examined	Per Cent Visualized	No. Examined	Per Cent Visualized
Iodopanoic acid.....	17	47	10	60	13	54	14	93
Cholografin.....	6	50	2	100	4	100	..	..

* When all infants under one year were grouped together and the two methods compared $P = < 0.0005$, i. e., this is a significant difference.

bility with relaxation of the sphincter of Oddi or the infantile spiral valve of Heister in the cystic duct, which does not keep the cystic duct open. In the latter condition dye then in the hepatic duct cannot enter the gall bladder.

Hrdlicka and co-workers,[8] using iodoalphionic acid (Priodax) orally (0.5-1.5 gm. per kilogram) and taking roentgenograms at 12, 14, and 16 hours, were not able to visualize the gall bladder in any infant under 6 months of age. They were able to visualize 50% of the gall bladders in 4 infants 6 months to 1 year of age; 75% in 4 infants 12 to 18 months; 60% in 5 infants 18 to 24 months; 50% in 8 children 2 to 4 years, and 94% in 16 children 4 to 11 years.

Harris and Caffey,[9] using iodopanoic acid (Telepaque) and iodoalphionic acid in the same dosage as Hrdlicka, were able to visualize 60% of the gall bladders in 20 infants less than 3 years of age. The gall bladders were visualized in 6 of 12 infants less than 6 months of age. Cholecystograms were most distinct in the majority of cases between four and nine hours after administration of the contrast material.

The work done in the Harriet Lane Home was begun with oral triturated iodopanoic acid, which was added to the evening formula in a dosage of 0.5-1.0 gm. These infants were not given anything by mouth for nine hours before the roentgenograms were taken. A double dose was given when the gall bladder failed to visualize, and the examination was repeated. No toxic reactions were encountered. Fifty-four infants were examined (Table 1). Cholecystograms of satisfactory quality were obtained in 8 of 17 infants less than 3 months of age. As age increased, better results were obtained, 60% visualization in infants 3 to 6 months of age, 54% at 6 months to 1 year, and 93% from 1 to 2 years. Two had biliary atresia, and their gall bladders were not visualized. With the above technique we were able to visualize the gall bladder of an infant 6 days of age, using an oral dose of 1.0 gm.

Our attention was directed to Cholografin with the hope that it might have some use in delineating the hepatic ducts in infants suspected to have congenital biliary atresia. We first attempted cholecystograms and cholangiograms in three rabbits, using 0.6 cc. of 20% Cholografin per kilogram intravenously. This was based on a 40 cc. dose for a 70 kg. adult. Double and triple doses were also used, and roentgenograms were taken at 10, 20, and 30 minutes and 1 and 2 hours. The gall bladders were visualized in situ in the rabbits receiving the largest and smallest

Fig. 1.—Rabbits were killed two hours after injection of Cholografin, and the livers and gall bladders were removed and x-rayed. No extrahepatic ducts are seen. Gall bladders of Nos. 1 and 3 visualized in situ. No. 2 was not visualized. Note how the gall bladder in 2 is embedded well within the liver and is still visualized poorly even though the contrast material has been concentrated there.

TABLE 2.—*Cholecystograms with Intravenous Cholografin*

History No.	Sex	Weight, Gm.	Race	Diagnosis	Age, Mo.	Dose Cholografin, Cc.	Factors	Exposures, Time: Min. 10	20	30	40	45	50	Hr. 1	2	3	4	5	Remarks
Rabbits No. 1	..	Approx.	...	.....	..	0.6	.....	0	0	0	..	..	..	0	+	..	..	..	Did not visualize in situ;
(litter No. 2	..	1,000	...	.....	..	1.2	.....	0	0	0	..	..	..	0	0	..	..	..	Fig. 1
mates) No. 3	..	.....	...	.....	..	1.8	.....	0	0	0	..	..	..	0	+	..	..	..	
B-11320	F	6,300	W	Hydrocephalus	9	7 (area)	20 ma. 58 kv.	0	0	0	..	..	..	0	+	..	..	..	Preparation—nothing by mouth
B-5851	F	9,790	W	Meningomyeloecele; Arnold-Chiari syndrome	8	6 (wt.)	20 ma. 58 kv.	0	0	+	..	..	..	+	+	..	..	..	Hiccups after injection; preparation—nothing by mouth
B-12970	F	12,450	W	Meningomyelocele	8	7.3 (wt.)	20 ma. 65 kv.	..	0	0	0	..	0	+	+	..	..	..	Preparation—nothing by mouth
B-11929	M	7,300	W	Hydrocephalus	7	5 (wt.)	20 ma. 56 kv.	..	0	+	+	..	+	+	+	..	..	..	No preparation
B-12895	F	3,750	N	Feeding problem	5	2.3 (wt.)	20 ma. 56 kv.	..	..	0	..	..	..	+	+	..	..	..	Preparation—nothing by mouth
B-12998	M	2,950	N	Diarrhea; premature	2½	1.8 (wt.)	20 ma. 56 kv.	..	..	..	..	0	..	+	+	..	..	..	Preparation—nothing by mouth
B-12918	F	5,260	N	Diarrhea	5½	3.2 (wt.)	20 ma. 56 kv.	..	..	..	..	..	..	0	+	..	..	..	No preparation
B-12883	M	3,700	N	Convulsions	2½	2 (wt.)	20 ma. 55 kv.	..	..	.	.	0	.	0	0	..	..	..	No preparation; did not visualize
							20 ma. 55 kv.	..	..	..	..	..	..	..	+	+	+	..	Days later examination repeated with double dose; no preparation
B-13786	F	3,310	N	Diarrhea	39 days	4 (wt.)	20 ma. 56 kv.	..	..	..	..	..	..	..	±	±	0	0	Double dose; poor visualization; gas shadows in bowel overlying gall bladder; no preparation
B-13120	F	2,870	N	Pyloric stenosis	1½	3.5 (wt.)	20 ma. 56 kv.	..	..	..	..	..	..	..	0	+	+	..	No preparation
B-12634	M	2,045	W	Premature	½	1.3 (wt.)	20 ma. 56 kv.	..	..	0	..	..	..	0	0	0	..	..	No preparation; did not visualize
						1.5 (wt.)	20 ma. 56 kv.	..	..	..	..	..	..	..	0	0	0	..	Repeated with double dose; no visualization; no preparation
B-12165	M	2,700	N	Inspissated bile syndrome	2	3.7 (wt.)	20 ma. 56 kv.	..	..	..	..	..	..	..	0	0	0	0	No preparation; did not visualize; double dose

doses at two hours. All animals were killed and the livers and gall bladders removed and x-rayed. All three then showed sufficient contrast medium in the gall bladder; no hepatic ducts were visualized at any time (Fig. 1).

Two infants were then given the drug in a dosage calculated in one by weight, as above, and in another by using body surface area. No essential difference was noted in the results, and thereafter dosage was calculated at 0.6 cc. per kilogram. A double dose was used with no ill effect for infants whose gall bladders were not visualized on the initial examination. The first infants studied were given nothing by mouth for four to six hours before Cholografin was injected, but later infants received the contrast material between feedings. A subcutaneous skin test was done to rule out sensitivity to the drug, and the Cholografin then was injected slowly over a five-minute period.

Both posteroanterior and left anterior oblique views were taken on the first few infants. Only posteroanterior views were taken in later studies, as the oblique view proved of little value because of overlying gas shadows. As motion was a prime problem a 0.1 second exposure was employed with 200 ma., a 40 in. (102 cm.) focal film distance, and a Potter-Bucky diaphragm. A range of 54 to 65 kvp was used. Initially films were taken at intervals of 10 minutes after injection of the Cholografin. As more experience with the drug was obtained and owing to the failure to demonstrate the hepatic ducts with these early films, exposures were made at one, two, three, and four hours.

No phlebitis or inflammation was noted at the sites of injection. The small amounts extravasated into the tissues caused no damage. No untoward reactions were encountered with Cholografin, nor were any later toxic effects seen. One infant developed hiccup of short duration.

Sufficient concentration of Cholografin to render the gall bladders radiopaque appeared within 30 minutes to 4 hours. Cholecystograms of diagnostic quality were obtained on the first attempt in 8 of 12 infants (Tables 1 and 2, Fig. 2). The gall bladder in a ninth infant was visualized when a double dose was used. The gall bladder in a 39-day-old infant was poorly visualized as a result of overlying gas shadows in the bowel; this film was interpreted as not being satisfactory for diagnostic purposes. The gall bladders were not visualized in a premature infant and in an infant with inspissated bile syndrome. In none were the extrahepatic ducts seen. All of the infants were under one year of age, and eight were under 6 months. The youngest infant was one-half month of age.

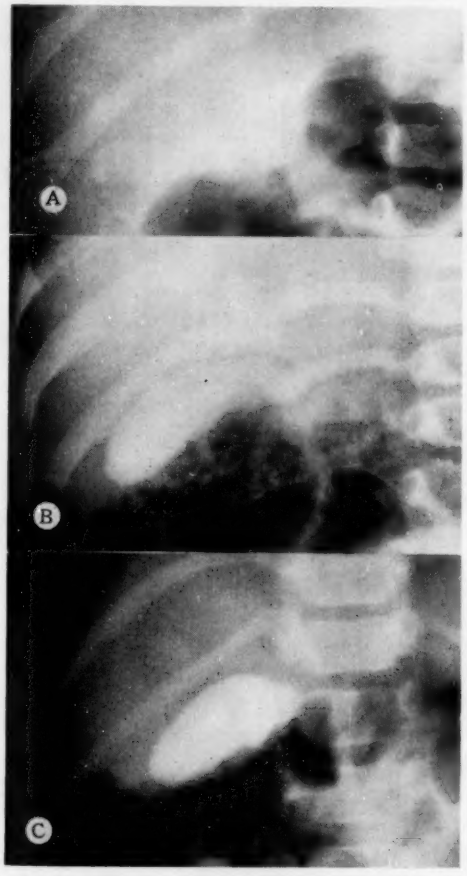

Fig. 2.—Cholecystograms. *A*, infant, 1½ months of age, posteroanterior projection, 1.2 cc. of Cholografin per kilogram at four hours. Note how the gall bladder is almost obscured by the liver shadow. *B*, infant 7 months of age, posteroanterior view, 0.6 cc. per kilogram at two hours. *C*, infant 5 months of age, same projection, 0.6 cc. per kilogram at two hours.

In no cases was there evidence that the material was being excreted by the kidney.

It is our view that Cholografin presents an excellent agent for cholecystography in infants. It is easily injected, with little tissue reaction, and is rapidly excreted by the liver of infants in less time than any other contrast material. Because of its high iodine content, sensitivity reactions will probably be encountered in allergic patients, but no untoward reactions were encountered in our small series. Infants are able to excrete contrast material in sufficient quantity to render the gall bladder radiopaque. This function appears to improve as the infant matures. The degree of success of cholecystography in infants is probably somewhat greater than that obtained with any contrast material previously used.

SUMMARY

Oral triturated iodopanoic acid in a dose of 0.5 to 1.0 gm. gave satisfactory results in 47% of the gall bladder series in 17 infants under 3 months of age. Fifty-four infants up to 2 years of age were examined; 63% visualized their gall bladders. The youngest in which the gall bladder was visualized was 6 days of age.

Intravenous Cholografin in dosage of 0.6-1.2 gm. per kilogram gave satisfactory cholecystograms in 9 out of 12 infants, or 75%, under 8 months of age, 8 were less than 6 months of age. The youngest in which the gall bladder was visualized was 1½ months of age. Visualization took place 30 minutes to 4 hours after injection. The extrahepatic ducts were not seen in any infant.

No untoward reactions or toxic effects of the drugs were encountered in either series. Infants are able to excrete contrast material from the liver. As the infant matures this function appears to improve.

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Methylbenzethonium Chloride in the Care of Skin of Infants and Children

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Diaper rash (ammonia dermatitis) has been demonstrated to be caused by urea-splitting organisms which act on the urine to produce ammonia.[1] Several antiseptics have been reported to be effective against these bacteria.

The reports * that poisoning of infants occurred by transcutaneous absorption of boric acid used as an ointment or powder on areas of diaper rash stimulated us to make a further selective evaluation of the toxicity and efficacy of the antiseptic methylbenzethonium chloride in controlling diaper rash and intertrigo. Available commercially,† the antiseptic was studied in the form of a dusting powder‡ and in an ointment.§

GENERAL PLAN OF STUDY

Methylbenzethonium chloride diaper rinse and the ointment were already patch-tested and reported on.‖ The following plan of study was therefore adopted.

1. Bacteriological studies against urea-splitting organisms of corn starch and 1:1800 methylbenzethonium chloride applied as a dusting powder.

2. Sensitivity studies of dusting powder applied to skin and when inhaled.

3. Clinical studies to evaluate this antiseptic baby powder (alone, with the base only, and with the diaper rinse) in the prevention and treatment of ammonia dermatitis (diaper rash) and of intertrigo, plus clinical testing of the ointment, with and without the antiseptic.

A. *Bacteriological Studies.*—Seven sterile diapers were dusted freely with the baby powder. A piece of filter paper was placed on each diaper and the paper was saturated with 10 cc. of urine heavily inoculated with Bacterium ammoniagenes. The diapers were wrapped in brown paper and incubated for 48 hours. The same procedure was repeated with diapers which had been dusted with a borated talcum powder (control powder). After 48 hours the packages were opened.

Four halves of the filter paper in four different diapers were placed in 100 cc. of sterile water. One, two, and three loopfuls of each flask were streaked on plates of nutrient agar. After incubation for 96 hours the plates were examined with the following results:

No.		Colonies
1	Control powder	290
	Test (methylbenzethonium chloride with cornstarch)	19
2	Control powder	600
	Test (methylbenzethonium chloride with cornstarch)	40
3	Control powder	1000
	Test (methylbenzethonium chloride with cornstarch)	60

The growth of B. ammoniagenes was thus demonstrated to be markedly inhibited in those diapers dusted with the test baby powder, but there was luxuriant growth of organisms in those control diapers dusted with 5% borated talc, or the cornstarch without the antiseptic.

B. *Sensitivity Studies.*—(*a*) Fifty healthy infants and children ranging in ages from 3 weeks to 5 years were skin-tested with patches treated with methylbenzethonium chloride powder. The patches were left in contact with the skin for 48 hours. One child developed an erythema which cleared in 48 hours. All the other children showed

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* References 2 and 3.

† Methylbenzethonium chloride was supplied as Diaparene Chloride by the Pharmaceutical Division of Homemakers' Products Corporation, New York 10, N. Y.

‡ Hardy, L. M.: Personal communication to Homemakers' Products Corporation, Dec. 8, 1952.

§ References 6 and 7.

‖ References 4-7.

no skin reaction. When the patch tests were reapplied after 10 days on the same children no reactions were noted.

(*b*) Ten adult rats on a stock diet were exposed to methylbenzethonium chloride dusting powder and to 5% borated talc in the following manner. An insufflator using a laboratory compressed air pump was led to a glass funnel under which each rat was placed. On exposure to the powder the rats made attempts to escape. After a few seconds they cowed into a corner for the 10 minutes of exposure to the powder. There were no reactions such as struggling, licking or pawing movements, conjunctivitis, respiratory difficulties, or convulsions with either methylbenzethonium chloride dusting powder or 5% borated talc.

C. *Clinical Studies.*—Two hundred infants 3 months to 2 years of age, with ammonia dermatitis, were treated with methylbenzethonium chloride powder.

(*a*) The criteria for diagnosis of ammonia dermatitis were location (areas of skin in contact with urine-soaked diapers or bed clothes), type of rash (mild, erythema; moderate, papular vesicular, pustular; severe, ulceration including meatus ulcer), and ammonia odor. The criteria for diagnosis of intertrigo were location (folds of skin, especially the groin), type of rash (erythema and exudation limited to the folds), and type of infant (usually obese infants improperly cleaned and bathed).

(1) Fifty infants were treated with methylbenzethonium chloride powder alone. The powder was dusted on the infant after each diaper change and at bedtime (an average of seven times a day). The diapers were washed with a mild soap and rinsed thoroughly. Diapers were changed usually within one-half hour after soiling except during sleep.

(2) Fifty infants were treated with methylbenzethonium chloride powder, as above, plus methylbenzethonium chloride tablets rinsed into the diapers.

(3) Fifty infants were treated with methylbenzethonium chloride powder, as above, plus methylbenzethonium-chloride-rinsed night diapers only, two such diapers being placed on the infant and left on throughout the night until normal awakening the following morning.

(4) Fifty infants were used as controls. These infants were dusted freely after each diaper change and at bedtime with a commonly used cornstarch not containing methylbenzethonium chloride. The diapers were washed with a mild soap and rinsed thoroughly.

All infants were treated for 10 days. The results are found in Table 1.

(*b*) The efficacy of methylbenzethonium chloride in a cornstarch base and a control powder was investigated in the treatment of intertrigo using 100 infants 3 months to 2 years of age as subjects (Table 2). Fifty infants were treated with methylbenzethonium chloride powder after each diaper change and at bedtime (an average of seven times a day). These were alternated with 50 infants similarly treated with a control powder. Routine skin and diaper care was observed.

D. *Efficacy of Ointment for Ammonia Dermatitis.*—One hundred infants were studied over a three-month period. Alternate infants were treated with methylbenzethonium chloride ointment or the base without the active ingredient, methylbenzethonium chloride. In all cases the ointment was applied after each diaper change and on retiring for the night (an average of seven times a day). The results are shown in Table 3.

TABLE 1.—*Results of Dusting-Powder Treatment of Ammonia Dermatitis*

Methylbenzethonium chloride dusting powder only		50
Cleared	39	
Unimproved	11	
Methylbenzethonium chloride dusting powder plus all methylbenzethonium-chloride-rinsed diapers		50
Cleared	49	
Unimproved	1	
Methylbenzethonium dusting powder plus methylbenzethonium-chloride-rinsed night diapers only		50
Cleared	47	
Unimproved	3	
Control powder		50
Cleared	23	
Unimproved	27	

TABLE 2.—*Results of Dusting-Powder Treatment of Intertrigo*

	Cleared	Unimproved
50 cases (methylbenzethonium chloride powder)	46	4
50 cases (control powder)	42	8

TABLE 3.—*Results of Ointment Treatment of Ammonia Dermatitis*

	Cleared	Unimproved
50 cases (methylbenzethonium chloride ointment)	41	9
50 cases (base without methylbenzethonium chloride)	21	29

COMMENT

This study corroborates the findings of other investigators that methylbenzethonium

chloride has a high bactericidal effect against B. ammoniagenes with absence of toxicity or allergenicity. Nagamatsu and co-workers [9] reported no toxic, irritating, or allergic reactions in extensive animal studies. Hardy ¶ found the dusting powder to be hypoallergenic and effective in comparing it and its cornstarch base in 57 cases of ammonia dermatitis.

Methylbenzethonium chloride is most effective when the water-miscible ointment or powder is combined with methylbenzethonium-chloride-rinsed diapers. The powder and ointment are slightly less effective without the diaper rinse, apparently because they are washed away from the skin with each urination. The results of using the powder on intertrigo and the skin irritations associated with the care of orthopedic or fracture cases with casts were good.

There seems to be no practical antiseptic effect of 5% borated talc against urea-splitting organisms. Therefore, aside from any debate as to its toxicity, we concur that 5% borated talc is not indicated for ammonia dermatitis.#

An interesting marginal note in our clinical experience is the increasing frequency of contact dermatitis due to inadequate home rinsing of detergents and soaps from laundered diapers. This condition was noted among our rejected cases (not ammonia dermatitis) where an antiseptic protective coating, such as Peri-Anal Creme,* was indicated.[8]

SUMMARY

The efficacy of methylbenzethonium chloride as a dusting powder and water-miscible ointment was evaluated in ammonia dermatitis (diaper rash).

The powder proved about 80% effective and the ointment 85% when each was used alone. When combined with methylbenzethonium-chloride diaper rinse, the efficacy approximated 100%.

There was no demonstrable toxicity or allergenicity in the concentrations used in any of the forms tested.

Methlybenzethonium chloride baby powder also proved to be effective in treating intertrigo and appears to be of value in the skin care in orthopedic and fracture cases in casts.

¶ Hardy, L. M.: Personal communciation to the authors, Dec. 8, 1952.

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* Supplied as Diaparene Peri-Anal.

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Effect of Corticotropin on Activity of Adrenal Cortex of Newborn Boy

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It has long been observed that the adrenal cortex of the newborn child differs morphologically from that of the older child or the adult. With the advent of corticotropin (ACTH) and more precise analytical procedures, studies were initiated to determine whether the adrenal cortex of the newborn infant responds as actively to stress as does the older child or the adult.

Klein and Hanson [1] reported less response to corticotropin in infants during the first week of life than in infants over a week old, as determined by the eosinophile response. However, Bergstrand and co-workers [2] have challanged the validity of the eosinophile measurements as evidence of adrenocortical activity. Read and co-workers [3] administered corticotropin to infants and determined adrenocortical activity by measuring the urinary output of 17-ketosteroids and corticosteroids. They observed a response to corticotropin in the newborn infant when sufficient hormone was injected. However, only 10 infants were used, and the corticotropin preparations were arbitrarily standardized and administered.

Consequently, it was decided to select a larger group of clinically well newborn babies and to study the response of the adrenal cortex to known amounts of corticotropin by determining the variation in the urinary excretion of the 17-ketosteroids and of potassium as well as changes in the plasma protein and potassium levels. It was expected that an increase in adrenocortical activity would be reflected by an increase in the excretion of the 17-ketosteroids and of potassium and by a decrease in the plasma proteins and the plasma potassium.

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METHODS

Four groups of clinically well newborn babies 1 to 5 days old were chosen for study. The babies were all boys, to facilitate the collection of urine specimens. The first group consisted of 10 babies. It was impractical to obtain 24-hour urine specimens, since the infants are brought to their mothers during the day. However, since infants void frequently, it was felt that a specimen collected over an eight-hour period could be considered representative.

At 10 p. m. a rubber cot was inserted over the penis. The rubber cot was secured by means of Scotch tape and adhesive and was attached by means of a rubber band to a piece of glass tubing leading into a catheter which then led into a urine bottle. This is illustrated in the Figure. Urine was collected until 6 a. m. the following morning, the 2 a. m. feeding being omitted. On this and on all succeeding urine specimens the total 17-ketosteroids were determined by a modification of the method of Zimmerman and co-workers,* and the potassium by the flame photometer.

At 8 a. m. of the same day, capillary blood from the heel was collected in heparinized capillary tubes as described in a previous publication.[6] Hematocrit readings were taken. One-tenth milliliter of the plasma was measured out for the potassium determination, while the total plasma proteins were determined on 0.03 ml. plasma by a micro modification of the biuret reaction. That same night, at 9:45 p. m., four to five units of corticotropin in gelatin solution were injected intramuscularly, and the entire outlined procedure was repeated, including urine collection starting at 10 p .m. that night and capillary blood specimens at 8 a. m. the following morning.

The second group consisted of eight newborn babies. Here the dose of cortropin-gel was doubled, 8 to 10 units being administered. In this group 48 hours instead of 24 hours were allowed to elapse

* References 4 and 5.

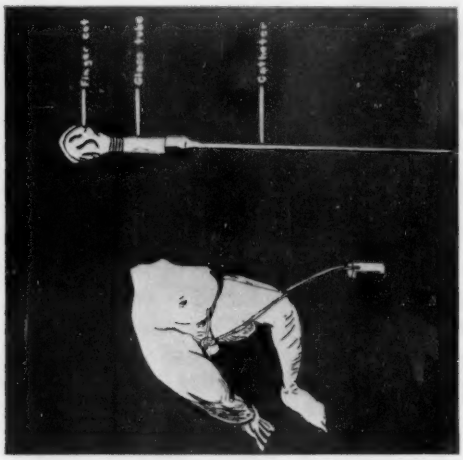

Illustration of the apparatus used for collecting urine from male infants.

in some of the babies between the collection of the first urine specimen and the administration of the corticotropin, with the subsequent collection of urine and blood.

Since a solution of corticotropin in gelatin is slow-acting, a third group of five newborn babies was taken and 10 units of an aqueous solution of corticotropin (Acthar, the Armour Laboratories), which is faster acting, was administered intramuscularly.

In order to determine whether any response obtained to corticotropin in the above three groups might not have been an artifact and have been due merely to the normal physiological development of the baby, a fourth group, consisting of five newborn babies, was studied. The same procedures and determinations carried out on the previous three groups were also performed on this group, either 24 or 48 hours apart, no corticotropin being administered.

RESULTS AND COMMENT

In the Table are listed the results obtained on 23 baby boys, 1 to 5 days of age, to whom corticotropin was administered. The plasma potassium revealed no consistent variation after corticotropin. A decrease, which would indicate an adrenocortical response, was observed in but four cases, with an increase occurring in seven cases. The levels were somewhat higher than in the case of adults. Of a total of 28 determinations without corticotropin, the values ranged from 3.98 to 6.98 mEq./L., with a mean of 4.95. Likewise, no consistent change in the plasma proteins after corticotropin administration was obtained. The plasma proteins were all within the normal range before corticotropin, with the exception of four cases which were low (less than 6.0 gm. per 100 cc.).

Sixteen of the 23 babies to whom corticotropin was given showed a significant increase in the urinary excretion of potassium. However, of the five babies (4a-4e) to whom no corticotropin was administered, all revealed an increase in the urine potassium after a lapse of 24 or 48 hours. Consequently, the increase in the urine potassium after corticotropin cannot be considered a positive adrenocortical response.

These same five control babies to whom no corticotropin was administered all revealed no increase in the urinary ketosteroids. In fact, four of the babies showed a decrease of 10%-45% after a lapse of 24 or 48 hours. Consequently, an increase, even small, in the urinary output of 17-ketosteroids must be considered an index of an increased response of the adrenal cortex to corticotropin. In evaluating the results in the Table, an increase of at least 20% in the urinary ketosteroids is considered a positive response. It is felt that this figure will take into account the error involved in the determination.

On this basis, 6 of 10 infants responded to corticotropin in Group 1, 4 of 8 infants in Group 2, and 2 of 5 infants in Group 3. This makes a total of 13 of 23 infants that showed an adequate response to corticotropin. These results also indicate that doubling the dose of corticotropin in gelatin had no effect on the ketosteroid excretion; while of the two corticotropin preparations used, the slow-acting solution in gelatin produced a more marked response than the faster-acting aqueous solution.

The results of the control group (4a-4e) indicate that a drop in the excretion of the ketosteroids is to be considered normal in the age group studied and may be attributed to the fact that the entire source of the 17-ketosteroids is not the infant himself. Part found in the urine may be maternal in origin.

In contrast to the evidence presented by other investigators, such as Bongiovanni,[7]

Comparison of the Urinary 17-Ketosteroids, Urinary Potassium, Blood Hematocrit, Plasma Potassium, and Plasma Proteins, Before and After the Injection of Corticotropin

	Before Corticotropin Administration							4-5 Units of Corticotropin in Gelatin Solution Injected Intramuscularly						
Child	Age, Days	Urine Excreted 10 p.m.-6 a.m., Ml.	17-Ketosteroid Excreted, Mg.	Urinary K Excreted, Mg.	HCT., Per Cent	Plasma K, mEq./L.	Plasma Protein, Gm./100 Cc.	Age, Days	Urine Excreted 10 p.m.-6 a.m., Ml.	17-Ketosteroid Excreted, Mg.	Urinary K Excreted, Mg.	HCT., Per Cent	Plasma K, mEq./L.	Plasma Protein, Gm./100 Cc.
1a	2	11	0.91	27.5	69	4.95	6.55	3	100	1.80	75.0	68	5.05	6.55
1b	1	73	0.64	29.0	47	4.27	5.59	2	76	0.94	45.6	45	4.55	6.25
1c	2	36	0.41	18.0	62	4.25	6.05	3	60	0.66	30.0	64	5.15	5.59
1d	3	83	0.60	37.0	61	4.75	6.55	4	70	0.83	34.2	60	4.85	5.59
1e	2	9.5	0.34	14.0	62	5.36	6.53	3	42	0.41	25.8	62	5.28	5.06
1f	1	17	0.53	23.8	62	4.83	5.82	2	24	1.10	28.8	62	5.42	7.00
1g	2	65	1.20	49.4	59	5.14	6.78	3	84	0.92	57.0	57	5.04	6.53
1h	3	50	0.72	42.5	50	5.30	6.05	4	103	0.94	93.8	52	5.38	6.65
1i	1	12	0.76	8.8	51	4.36	6.31	2	86	0.72	66.0	56	4.70	6.84
1j	2	8	0.61	12.0	69	4.82	7.22	3	30	0.64	69.0	56	4.40	7.34
								8-10 Units of Corticotropin in Gelatin Solution Injected Intramuscularly						
2a	2	61	0.67	14.6	69	5.58	6.41	4	130	0.87	58.5	61	5.08	6.59
2b	2	24	0.55	14.4	60	5.58	6.84	4	30	0.69	20.8	58	5.96	6.84
2c	1	26	0.62	63.4	53	5.30	6.34	3	32	0.62	33.0	50	6.38	6.34
2d	2	37	0.59	34.0	65	5.62	7.12	4	39	0.67	40.3	55	5.82	6.84
2e	2	10	0.80	13.0	58	6.18	6.03	4	85	1.10	70.0	60	6.22	6.66
2f	1	5	0.45	6.1	69	5.48	6.19	2	33	0.49	14.5	78	5.79	6.31
2g	2	35	0.69	28.7	61	5.90	5.66	3	49	0.78	40.6	58	5.68	6.03
2h	3	13	0.33	9.7	63	5.42	5.78	4	38	0.40	43.7	61	6.20	5.60
								10 Units of Corticotropin in Aqueous Solution Injected Intramuscularly						
3a	3	65	0.65	32.5	67	6.24	5.40	4	52	0.85	48.4	62	6.20	5.28
3b	1	8	0.46	13.6	62	5.34	7.68	2	6	0.40	12.1	60	4.92	7.12
3c	3	40	0.78	16.0	45	5.04	6.84	4	80	1.50	61.6	45	5.06	6.84
3d	3	92	0.62	21.2	56	5.02	6.31	4	52	0.65	27.0	52	4.56	6.44
3e	1	11	0.82	22.6	60	5.26	7.68	2	75	0.80	29.8	56	5.10	7.91
								No Corticotropin Administered						
4a	3	17	0.52	11.1	68	5.66	7.12	4	16	0.33	19.2	60	5.68	6.84
4b	2	27	0.96	12.7	62	3.98	6.03	4	50	0.52	21.0	60	4.06	6.31
4c	2	17	0.88	17.0	57	5.16	6.56	3	57	0.86	35.3	58	5.42	6.78
4d	2	30	0.67	12.0	70	5.02	6.36	3	65	0.48	29.9	66	5.10	6.38
4e	2	55	0.94	39.2	55	6.30	6.31	4	77	0.83	69.3	52	6.20	6.80

that extremes of urine volumes may affect 17-ketosteroid excretion, no such results were obtained in this study. Control group 4a-4e reveals that in four cases where the urine volume was increased anywhere from 40% to 300%, the 17-ketosteroid excretion either remained unchanged or decreased. In no case was there an increase in ketosteroid excretion with an increase in urine volume.

SUMMARY

The activity of the adrenal cortex of 23 newborn baby boys 1 to 5 days old was studied by injecting corticotropin and collecting urine samples for 17-ketosteroid and potassium excretions and blood samples for plasma potassium and protein levels. Five babies to whom corticotropin was not administered were used as controls.

Of the above tests, only the urinary excretion of 17-ketosteroids indicated a positive response to corticotropin. This was obtained in 13 of the 23 baby boys.

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Congenital Renal Tubular Dysfunction (Nephrogenic Diabetes Insipidus)

Report of a Case Complicated by Calcifications in the Renal Pedicle

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In their discussion of diabetes insipidus, Holt and McIntosh [1] consider the pathogenesis of this syndrome as being due to either intracranial pathology, a defect in renal function, or a spurious diabetes insipidus due to transient excessive fluid intake. In recent years several unusual cases of polyuria unaffected by vasopressin injection (Pitressin) have been described. They have been reported under various titles, such as "A Congenital Defect of Water Metabolism"[2]; "Nephrogenic Diabetes Insipidus"[3]; "Congenital Diabetes Insipidus Resistant to Treatment with Pitressin,"[4] and "Diabetes Insipidus in Infancy Resistant to Pitressin."[5] All of these cases represent instances of diabetes insipidus in which excessive volumes of urine of low specific gravity are excreted due to defective renal tubular physiology.

This report deals with a new member of the family discussed by Williams and Henry (Fig. 1) who had, in addition to the functional renal disability, peculiar calcific deposits in the right kidney pedicle.

REPORT OF CASE

S. N., a white boy born July 30, 1951, was first seen in the office (by L. J. F.) at the age of 2 weeks because of failure to gain weight. Normal

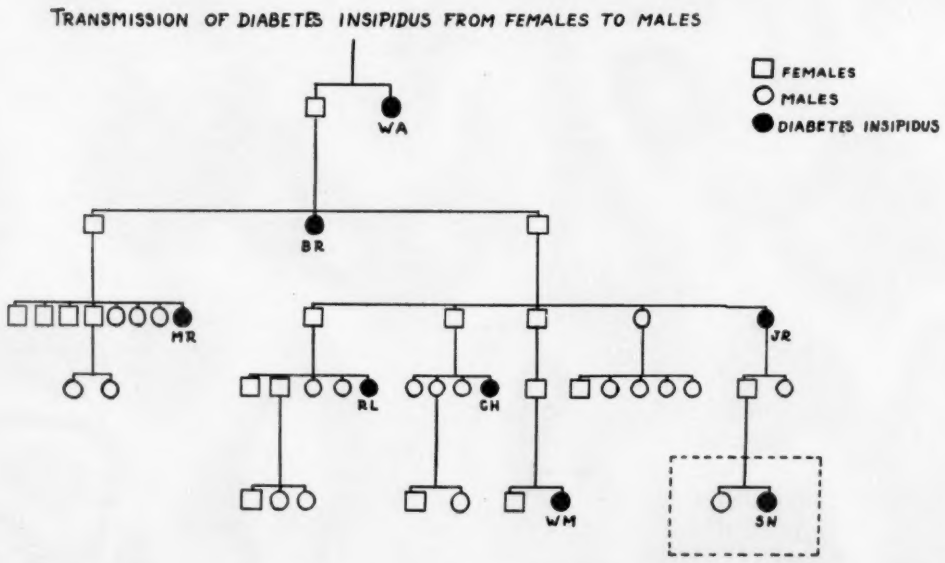

Fig. 1.—Family tree of patient S. N. Dotted portion has been added to chart from article by Williams and Henry. Reproduced with permission from Williams, R. H., and Henry, C.: *Annals of Internal Medicine*, American College of Physicians, Lancaster, Pa.

delivery at term followed an uneventful pregnancy. The birth weight was 7½ lb. (3400 gm.). At first he was breast-fed, but because he did not suck well he was placed on formula. It was noted at one month of age that he had a low-grade fever and appeared to be somewhat dehydrated. At 2 months of age, because of recurring vomiting, diarrhea, and fever, he was admitted to Denver Children's Hospital. The patient's mother was convinced by this time that her infant was a "water baby." This term had been used by her family for several generations to describe afflicted members.

Physical examination revealed a seriously ill, dehydrated, and marasmic infant. The skin was pale and of poor turgor. The temperature was 100.6 F., height 22½ in. (57.2 cm.), and weight 8 lb. 12½ oz. (3980 gm.). He appeared to be acidotic and in a state of collapse. His blood CO_2-combining power was 16 mEq/liter; serum chlorides, 119 mEq/liter; serum sodium, 166 mEq/liter; serum potassium, 5.0 mEq/liter; N. P. N., 68 mg/100 ml.; serum calcium, 11 mg/100 ml; serum phosphate, 7.1 mg/100 ml., and serum alkaline phosphatase, 27.7 Bodansky units. Erythrocytes 2,900,000; hemoglobin 10.5 gm. per 100 cc.; white blood cells 11,500; 35% granulocytes; 62% lymphocytes; 3% monocytes. Repeated blood cultures were negative. Urinalysis on admission showed specific gravity of 1.016, acid reaction, negative for sugar and albumin, and sediment showed an occasional white cell. Twenty-four-hour urine collection showed an average of 1000 cc. per day, with a specific gravity never exceeding 1.010 and usually around 1.002.

With correction of fluid and electrolyte balance, the general condition improved. Multiple small blood transfusions were administered. There was an irregular febrile course with a temperature range from 98 to 103.8 F degrees; his temperature was normal only when the infant was getting at least 2000 cc. of fluid per day. At first the intake was supplemented parenterally, but as the child's condition improved he took increasing quantities of water by mouth in addition to his formula. It was amazing how much fluid this 2-month-old infant could consume. He would take 6 to 8 fluidounces (177.4 to 236.6 cc.) of formula followed in two hours by 6 to 8 fluidounces of water, and this continued around the clock. Excretion kept pace with the huge intake. Vasopressin tannate (Pitressin Tannate) given in doses of 0.2 cc. and 0.3 cc. intramuscularly did not diminish the large output, nor was there any change in urine specific gravity.

Films of the skull revealed no abnormality. Repeated intravenous urograms showed good excretion by the left kidney, which was thought to be slightly larger than average. On the right side a calcific density occupied the region of the renal pelvis (Fig. 2); excretion was poor, there being only a small amount of dye visualized in two major

Fig. 2.—Flat film of abdomen. Note unusual calcifications in area of right renal pelvis.

calyces. No dye was seen in the renal pelvis. Cystoscopy with the McCarthy miniature cystoscope was attempted, but obstruction encountered at the perineoscrotal juncture could not be passed. Because of the urographic findings it was felt that exploration of the right kidney was indicated, but surgery was deferred until the patient's condition could be improved. He was discharged from the hospital Oct. 22, 1951.

At home his mother allowed him to have fluids as he wished. His progress at first was encouraging, but after three weeks he again had difficulty in retaining fluids, and he became acutely ill and dehydrated. On Nov. 26, 1951, he was readmitted to the hospital. Large volumes of fluid were given parenterally, and again his condition improved. Arteriograms showed satisfactory arterial supply to both kidneys. Films made after injection of the medium showed good excretion by the left kidney, but the dye remained concentrated in the right renal parenchyma for a prolonged interval.

On Dec. 18, 1951, operation was performed through a loin incision. The right kidney was exposed and mobilized. Externally it was normal in appearance. The pelvis was opened and explored; no calculi were in it. Further exploration revealed the calcifications to be within the renal pedicle in the areolar tissue between the vessels. The calcifications were multiple small bodies, and as much of this material as was surgically possible was dissected out. Biopsy of the kidney revealed an intact renal capsule and normal glomeruli, and the proximal convoluted tubules showed cloudy swelling with

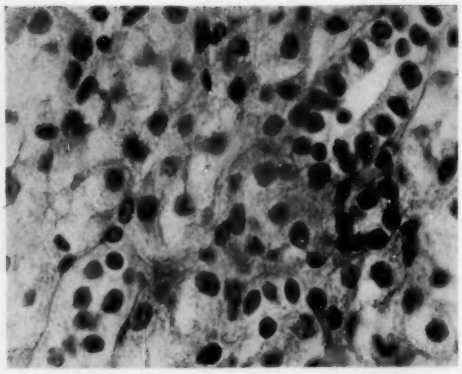

Fig. 3.—Renal biopsy; reduced slightly from mag. × 420. Note cloudy swelling of tubules.

fine eosinophilic debris in their lumens (Fig. 3). The remaining tubular elements revealed no changes. Vasculature was somewhat engorged. The calcific bodies were multiple and stone-like, averaging 1 to 2 mm. in diameter. Unfortunately, these were discarded before chemical analysis was completed.

The postoperative course was surprisingly uneventful. The patient was afebrile for three days before discharge from the hospital, on Dec. 29, 1951. His general condition was much improved, his weight having increased from 10 lb. 4½ oz. (4665 gm.) to 10 lb. 12½ oz. (4890 gm.).

At home he continued to take large volumes of fluid. He had occasional respiratory infections and intermittent bouts of fever, but continued to make slow improvement. At 10 months of age, he weighed 14½ lb. (6575 gm.). In April, 1952, intravenous urograms were repeated. The study was unsatisfactory because of poor concentration of the dye due to the patient's huge water demands. Following this procedure, the patient left our care because of change in residence. In October, 1952, urologic examinations with retrograde pyelograms were made by Dr. John Dougherty, in Knoxville, Tenn. Excretion of sodium indigotindisulfonate (indigo carmine) was fairly good from both kidneys (diuresis caused dilution of the dye). No calcification in the right kidney area could be seen. The pyelograms showed slight dilatation of the left kidney pelvis and blunting of the calyces with suggestion of a ureteropelvic constriction. The right kidney and ureter appeared normal. The bladder was of increased capacity. The latter finding has been described as a characteristic of diabetes inspidus.[7]

A report from the patient's mother stated that at 18 months of age he was consuming about 3½ quarts of water every 24 hours in addition to his milk, "so naturally he continues to urinate often."

COMMENT

In his original description of the syndrome, Waring listed the following clinical characteristics:

(1) onset shortly after birth, (2) erratic and unexplained fever, (3) persistent constipation, (4) vomiting (during the first three months of life), (5) polydypsia and polyuria, which do not respond to pitressin, (6) high value for serum sodium and chloride, (7) high skin resistances, (8) rapid dehydration if fluids are reduced or withheld, (9) inability to excrete urine of a high specific gravity, (10) familial incidence and (11) occurrence in boys only (?).

Clinical pathological studies have shown disturbances in renal function with alterations in blood chemistry due to dehydration, apparently resulting from failure of normal tubular reabsorption of water. Williams and Henry postulated that "there was a congenital defect in the loop of Henle as well as in the distal convoluted tubules but the glomeruli and proximal convoluted tubules were aparently normal." The derangement in water excretion is identical with that in diabetes insipidus except that vasopressin injection does not affect the diuresis. Wilkins[6] concluded that there is apparently a failure of response by the "end-organ" (renal tubule) to the antidiuretic hormone of the pituitary.

SUMMARY

A case of congenital renal tubular dysfunction (nephrogenic diabetes insipidus) is described. The patient presented an additional interesting feature, that of calcifications in the right renal area, which were in the interstitial tissues between the renal vessels. We postulate that the calcific bodies produced obstruction to the venous circulation of the kidney, causing additional interference with function of this kidney. Several months following surgery this kidney appeared to show no pyelographic deformity. The presenting clinical picture in this case as well as the others described in infants was that of pyrexia of unexplained etiology associated with vomiting, dehydration, and collapse. The diagnosis became evident when it was realized that the patient required tremendous

volumes of water to maintain fluid balance compatible with the kidney defect and that the associated diuresis was unaffected by vasopressin injection.

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News and Comment

GENERAL NEWS

Survey of Pediatric Education in Latin America.—The Pan American Sanitary Bureau, Regional Office for the Americas of the World Health Organization, is planning to conduct a Survey of Pediatric Education in Latin America, beginning in July, 1955, similar to those which have been carried out in the U. S. A., Canada, Europe, Australia, and New Zealand. The Latin American survey, which will cover 21 countries and approximately 75 schools, will take place in the fall of 1955 and will be under the general direction of Dr. Myron E. Wegman, Chief of the Division of Education and Training of the Bureau, and formerly Professor of Pediatrics at Louisiana State University. Dr. James G. Hughes, Professor of Pediatrics at the University of Tennessee, will act as special consultant for this program and will be visiting a large number of the schools.

Endorsement of the program has been given by the International Pediatric Association and the American Academy of Pediatrics, whose country chairmen and secretaries will be collaborating in the gathering of information.

"Recommended Standards for Cardiovascular Clinics."—Copies of "Recommended Standards for Cardiovascular Clinics" are available to members of health departments, clinic staffs, hospital trustees, and other professional personnel concerned with community health problems, from local Heart Associations or from the American Heart Association, 44 East 23d St., New York 10.

Case Reports

ANEURYSM OF THE RENAL ARTERY CAUSING HYPERTENSION

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ANEURYSM of the renal artery is a rare disease. Sharp and Green [1] reviewed the literature in 1950 and collected a total of 93 cases. Schwalbe [2] added the 94th case in the same year. Howard, Forbes, and Lipscomb,[3] in 1940, reported the only case in which an aneurysm of the renal artery caused hypertension of the Goldblatt type. The patient was a 5-year-old boy who apparently was cured of his hypertension by nephrectomy. A similar case is the subject of this presentation.

REPORT OF A CASE

S. A. H., a white girl 8 years of age, was admitted in an unconscious condition to the medical service of the Charles W. Wilson Memorial Hospital on July 29, 1953. According to the history obtained from the parents, the child had complained of headaches, off and on, for one year. She had suffered a minor head injury in March, 1953. X-rays of the skull at that time had been negative. The parents had also observed that the child had had urinary frequency and nocturia (three to four times a night) for several months. The patient had been otherwise well until 12 hours before her admission, when she began to complain of severe headache. She vomited about 15 times during the night and toward morning lost consciousness. On the way to the hospital she had generalized convulsions.

The past history was noncontributory except for an injury to the right hip and right lower abdomen, with abdominal subcutaneous hematoma, in 1952.

Examination revealed a well-developed semiconscious girl 8 years of age. Temperature 98.8 F, pulse 86 and regular, respirations Cheyne-Stokes in character. Blood pressure 150/130 mm. Hg. The pupils reacted to light, but the optic discs revealed blurring of the disc margins but no lobulation of the vessels, no hemorrhages, or exudates. There was no cervical rigidity. Heart and lungs were normal on physical examination. The abdomen was soft, and there were no palpable masses. The tendon reflexes could be elicited in the upper extremities but were absent in the lower extremities. There was a questionable Babinski reflex.

Laboratory Data.—Urinalysis revealed albuminuria 4+ with 8-10 leucocytes per Hpf. and was sterile on culture. Hemoglobin 90%, with red blood cell count of 4,580,000 per cm. White blood cell count was 11,400, with 90% neutrophiles and 10% lymphocytes. Fasting blood sugar was 115 mg. per 100 cc., nonprotein nitrogen 31 mg. per 100 cc., and CO_2 combining power 42 vol.%. The sedimentation rate was 20 mm. per hour. Spinal fluid pressure was over 600 mm. water, the cell count was 3 cells per cu. mm., total protein was 33 mg. per 100 cc., and sugar was 109 mg. per 100 cc. The electrocardiogram was normal. There was no decrease in blood pressure following piperoxan (benzodioxan) of phentolamine (Regitine). An excretory pyelogram showed a small nonfunctioning kidney on the right. There were two ring-shaped calcific shadows medial to the midportion of the right kidney. The left kidney was functioning satisfactorily and appeared normal. A stereoscopic x-ray of the abdomen showed that the calcifications were situated in a plane slightly anterior to the right kidney. Cystoscopy showed a normal bladder. A No. 4 catheter was easily advanced into the right renal pelvis. No urine was obtained. Retrograde pyelogram in an anteroposterior and right lateral position showed a very small but otherwise well-proportioned renal pelvis and calyces. The calcification was situated anterior to the kidney and seemed to be connected with the hilum (Fig. 1). Diagnosis: Calcified aneurysm of the right renal artery causing a Goldblatt type of hypertension.

Preoperatively the blood pressure ranged from 150/115 to 220/180 mm. Hg. The patient regained consciousness the day following admission but was lethargic and complained of headache. Nephrectomy was performed on Aug. 6, 1953. At operation, the aneurysm was felt as a hard irregular mass estimated at about 2×1×1 cm. in size. The lateral end was attached to the renal hilum by a soft pedicle measuring about 1 cm. in length. The medial end of the aneurysm was overlying the inferior vena cava, with which it was densely adherent. During the dissection of the medial end of the aneursym there was suddenly profuse bleeding from the depth of the wound. It was impossible to clamp the renal pedicle proximal to the aneurysm. Since the kidney obstructed the view of the bleeding area, the pedicle was quickly divided at its attachment with the aneurysm, the kidney was removed, and the wound

Fig. 1.—*A*, excretory pyelogram. *B*, retrograde anteroposterior retrograde pyelogram. *C*, right lateral retrograde pyelogram.

was packed. It was then possible to clamp and ligate the pedicle. Bleeding was then completely controlled with a continuous chromic absorbable surgical suture (gut), which was placed in the tissue containing the renal vessels. In spite of prompt replacement of blood, the blood pressure, which had been 220/170 mm. Hg at the start of the operation, dropped temporarily to 0 but returned to hypertensive levels at the end of the operation.

Postoperatively the patient did well, and the blood pressure stabilized at 130/60 mm. Hg. The urinary output during the first 12 hours after operation was 1300 cc. Then, after passing 150 cc. of bright red bloody urine, the patient became anuric. The N. P. N. rose to 52 mg. per 100 cc. Diuresis started 36 hours later, and from then on the postoperative course was uneventful, and the patient was discharged on the ninth postoperative day.

The patient is still under observation. She is asymptomatic. Urinalysis has been consistently

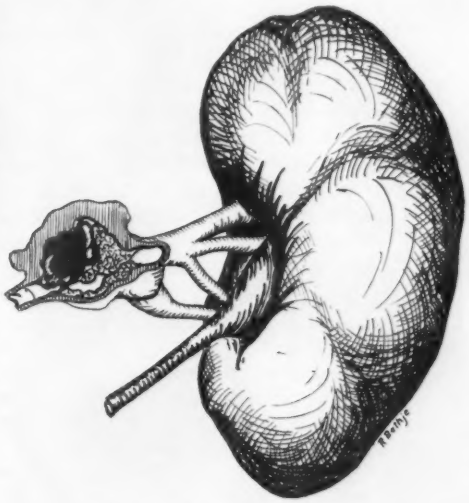

Fig. 2.—Drawing of specimen.

negative, and her blood pressure ranges around 95/60 mm. Hg.

Pathological Report (Dr. A. A. Kosinski).—The specimen (Fig. 2) consists of a kidney measuring 8×4×2.5 cm.; the outer surface is deep red and has irregular strands of fatty tissue attached to it. At the hilar region is a firm mass 2.0 cm. in diameter. Upon dissection the renal artery was found to be contiguous with this mass. Section of this mass proved it to be composed of calcified brownish-gray material. A small vascular channel was traced through this mass and found to be continuous with the distal segment of the renal artery. The capsule of the kidney stripped with ease, revealing a smooth tan surface. On cut section the corticomedullary demarcation was distinct, and the cortex measured 0.5 cm.; the medulla measured 1.5 cm. in width. The renal pelvis was of normal size and lined by a white glistening membrane.

Diagnosis.—Kidney (right) with focally calcified aneurysm of the renal artery and showing foci of early arterionephrosclerosis as well as a suggestion of glomerular atrophy.

Note.—There is considerable chronic inflammation in the outer layers of the aneurysm.

SUMMARY

A case of hypertension with hypertensive encephalopathy in an 8-year-old girl is presented. The apparent cause of the hypertension was renal ischemia associated with thrombosis occurring in an aneurysm of the right renal artery. Following nephrectomy, the blood pressure returned to normal levels.

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News and Comment

GENERAL NEWS

Children's Bureau.—The report (for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C.; price, 40¢) of the Task Force on Federal Medical Services of the Hoover Commission on Organization of the Executive Branch of the Government contains the following paragraph (p. 101) of interest to pediatricians regarding the Children's Bureau:

> The Children's Bureau is one of the few Federal agencies organized strictly on the basis of clientele. Founded in 1912 in a reform era, the Bureau has operated with dedication and with outstanding success. In 1946, when it was transferred from the Department of Labor to the Federal Security Agency (predecessor of the new Department), it was placed within the Social Security Administration.
>
> We conclude that the Children's Bureau does not logically belong in the Social Security Administration for it has important duties outside the welfare field. On the other hand, the work of the Bureau has been so satisfactory and its focus on the whole child so desirable that its functions should not be split among other constituent agencies of the Department.
>
> We believe that the Bureau should be continued intact, and elevated to a point where the Bureau Chief has access to the Secretary. We also favor giving the Bureau authority and appropriations to make research grants.
>
> The Task Force Recommends
>
> That the Children's Bureau be removed from the Social Security Administration and placed in an administrative position in the Department of Health, Education, and Welfare that will facilitate the major mission of the Bureau. This mission is to take cognizance of the needs of the whole child in the broad fields of health, education, and welfare, support necessary research in the field, and stimulate the utilization of new knowledge by the various agencies of the Federal Government within and outside the Department of Health, Education, and Welfare and in the States.

DIFFUSE HAMARTOMA OF THE UPPER LOBE IN AN INFANT

Report of Successful Surgical Removal

G. GRIMSLEY GRAHAM, Crossville, Tenn.
and
JACK W. SINGLETON, Hayward, Calif.

THE TERM hamartoma has been present in the literature since 1904. It denotes an abnormal mixing of the normal elements of an organ. It has been postulated that these tumors arise from the cartilage of the bronchial rings or have their origin in an embryonal anlage. The tumor has been reported as being present in various organs, however, the advance of thoracic surgery, and the vigorous attack on pulmonary carcinoma has altered the impression that this is a "rare" pulmonary lesion to that of an "unusual" one.

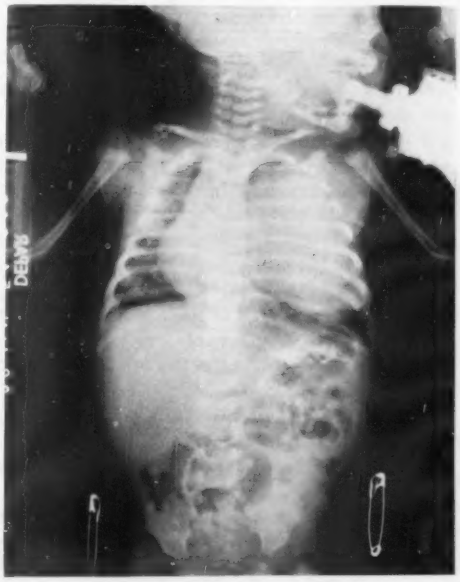
Ordinarily, hamartomas of the lung are well-circumscribed lesions that have to be distinguished from carcinoma of the lung, bronchial adenoma, hemangioma, granuloma, bronchogenic cyst, pulmonary abscess, and tuberculosis. This tumor is usually thought of as one of the "coin" lesions, and its main importance lies in the difficulty in trying to differentiate it from a malignant tumor through x-ray and clinical studies. The majority of reported cases have been adults. It is more commonly seen in males than in females. An estimated 60% [1] of the cases will have no symptoms referable to this pulmonary lesion. Among those with symptoms and signs cough is the commonest sign. This is difficult to evaluate in view of the large number of "cigarette coughs" present in the nation. Pain, dyspnea, and hemoptysis may be present.

The symptoms depend primarily on the size and location of the tumor. It is apparent that the more centrally located tumors will cause symptoms due to their mechanical obstruction. Less than 10% [2] of the reported cases of hamartoma involved a major bronchus; it is more commonly a peripheral pulmonary lesion. A true hamartoma of the lung is generally known to be benign and seldom undergoes malignant [3] degeneration.

Grossly, these tumors usually appear as encapsulated masses, varying from 1 to 6 cm. in size, brownish- to pinkish-gray in color, firm, and resistant to cutting. The microscopic picture is that of varying amounts of mesenchymal and epithelial elements surrounding cartilage (which may, may not be present).

It is extremely rare to have one of these tumors involve the greater part of a lobe. Moersch and co-workers [4] mention one case that involved most of the pleural cavity; Jones [5] reported a case in which the majority of the right upper lobe was replaced by hamartoma, his case being that of a newborn

Fig. 1.—Preoperative film, showing massive tumor in left chest, with mediastinal shift.



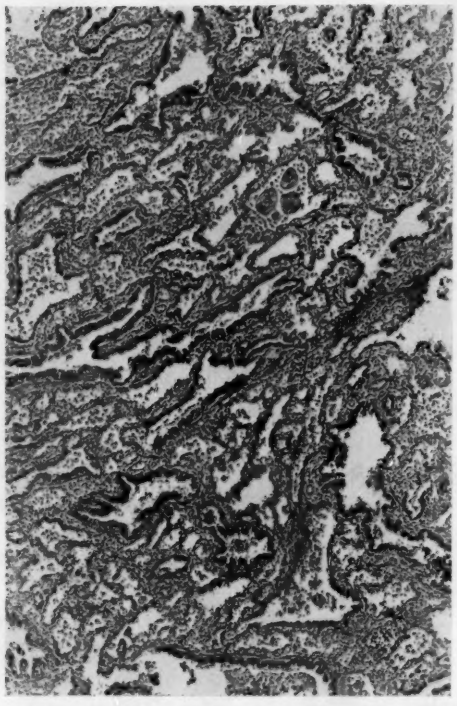


Fig. 2.—The hamartoma is seen to be composed of disorganized pulmonary components—bronchioles and alveoli. Both are markedly dilated and also have greatly thickened septa.

that died shortly after birth. Harris and Schattenberg [6] reported two peculiar "anlagen tumors" in the lungs of newborn infants.

REPORT OF A CASE

D. L. R., born Dec. 9, 1953. This firstborn baby girl was the product of a normal pregnancy, normal labor, and normal delivery. The birth weight was 7 lb. 4 oz. (3290 gm.). There was no difficulty in resuscitation, the infant cried immediately and lustily, and the color was normal. No respiratory disturbance, cyanosis, or dyspnea was noted during the neonatal physical examination or during the three-day stay in the nursery.

The patient was seen at the age of 2 weeks for a dacrocystitis; no abnormal symptoms were reported by the mother or noted by the doctor at that time.

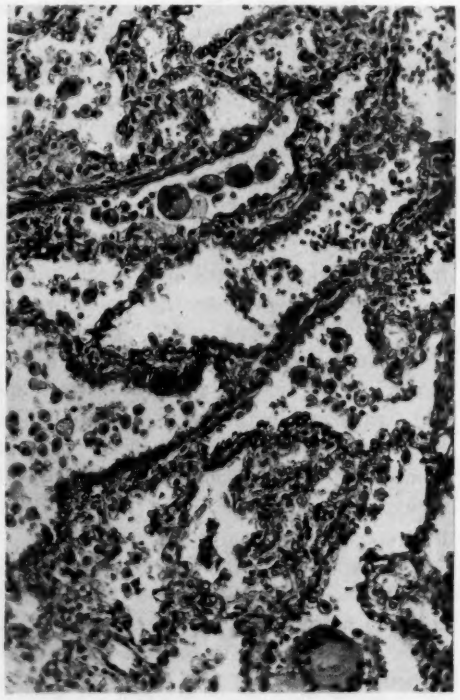
The infant was seen again at the age of 6 weeks for a regular well-baby check-up, and at that time the physician noted deep sternal retraction on inspiration, and the heart sounds were heard best over the right chest, with the P. M. I. being located in the midclavicular line. There were no respiratory distress, cyanosis, or abnormal heart sounds noted. Heart and respiratory rates were normal. Breath sounds were thought to be normal throughout both lung fields. Because of the normal position of the liver and spleen as determined by palpation, an isolated dextrocardia was thought to be present.

An x-ray was ordered, but before the results were available the infant was brought back to the Outpatient Clinic with a fever of 103 F rectal, persistent severe cough, occasional vomiting, and mild dyspnea. There was no cyanosis; sternal retraction was still present. Breath sounds over the left chest were decreased; coarse and fine moist rales were barely audible in the left chest. In the right chest the P. M. I. was again noted in the midclavicular line; heart sounds were normal. Breath sounds in the right chest were interpreted as normal, no rales were heard. A diagnosis of pneumonia with dextrocardia was made, and the infant was admitted to the hospital.

Laboratory data on admission revealed the hemogram to be as follows: WBC, 7,550; N. 33; L. 54; M. 13; RBC, 3,320,000, and Hgb., 9.5 gm.

The x-ray report revealed a homogenous density occupying the left hemithorax extending from the

Fig. 3.—Bronchioles lined by tall cuboidal and cellular epithelium. Some areas of the mucosa show cilia as well as globules of mucin. The exudate is predominantly lymphocytic, with only a few plasma cells and polymorphonuclear leucocytes. Scattered foreign-body giant cells are also seen.



region of the hilus. There was a shift of the mediastinal structures to the right, and the heart was noted to occupy the right hemithorax. Fluoroscopy revealed the mass to lie anteriorly and to extend from the mediastinum. No calcifications or pulsations in the tumor were noted.

Impression.—Probably a tumor arising from the anterior mediastinum; teratoma or dermoid cyst.

The infant was treated with penicillin, streptomycin, blood transfusions, and oxygen and improved promptly; she became afebrile, cough diminished, and rales cleared. Repeat x-rays revealed no change in the chest findings. An operation was performed at the age of 7½ weeks.

OPERATIVE NOTE

An exploratory thoracotomy through a posterolateral approach on the left was performed on Feb. 3, 1954. It was readily apparent that the preoperative diagnosis of a mediastinal tumor was in error. The entire left upper lobe was firm and somewhat rubbery in consistency, and the color was light pink. There were several large hilar nodes present. Examination of the left lower lobe was entirely negative. A left upper lobectomy was done in the routine manner. The infant tolerated the surgery without any difficulty and was returned to the ward in good condition. Her postoperative course was uneventful, and she was discharged from the hospital 15 days after surgery.

PATHOLOGY REPORT

Gross.—Left upper lobe measuring 9×7×3.9 cm. A small amount of aerated tissue was found around the periphery of the specimen, while the major portion felt firm and rubbery. The firm area was grayish-pink in color.

Microscopic.—Sections of the tumor mass show the alveolar septa to be thick-walled and fairly cellular. The alveolar spaces in the tumor mass appear dilated, and are lined by tall cuboidal or columnar epithelium. Some of these cells appear to have cilia present as well as globules of mucin. Many of these spaces resemble bronchioles of an immature type.

Pathology Diagnosis.—Hamartoma, lung, left upper lobe.

Since discharge she has been followed in the outpatient clinic and except for the development of a pes excavatus has continued to do well. On the most recent visit, at the age of 8 months, she weighed 15 lb. 3 oz. (6890 gm.) and was asymptomatic except for mild upper respiratory infection.

SUMMARY AND CONCLUSIONS

The literature on hamartomas is briefly reviewed. The reported cases have been primarily adults with small "coin" type lesions. This case is added because it represents the first reported successful removal of a large hamartoma involving the majority of a lobe in a young infant.

20094 E. 14th St. (Dr. Singleton).
Cumberland Clinic (Dr. Graham).

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ACUTE HEMOLYTIC ANEMIA DUE TO NAPHTHALENE INGESTION

EMANUEL CHUSID, M.D.
and
CHARLES T. FRIED, M.D., New York

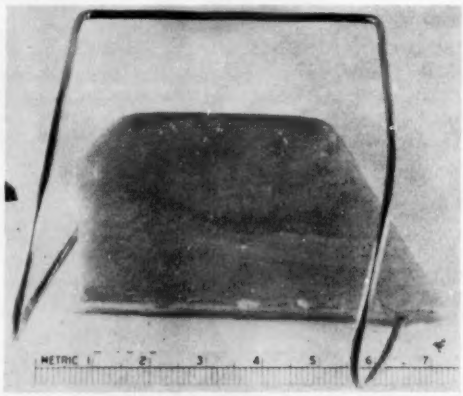
HEMOLYTIC anemia secondary to ingested naphthalene has only recently received attention in the American literature,* although the entity had been well described previously in world literature.† The first American report was by Zuelzer and Apt, in 1949, when they presented four cases of fulminating hemolytic anemia and, with the aid of dog studies, established this as a clinical entity.[1] Subsequently, there have been additional reports in this country, bringing the total number of cases to nine, all of which, directly or indirectly, were due to moth-ball ingestion or absorption.‡ We are aware of other cases as yet unreported.§

We are reporting this case primarily to show that other home products besides moth balls and flakes contain naphthalene and are thus potentially poisonous, and secondly to reemphasize the hemolytic toxicity of naphthalene.

REPORT OF CASE

R. A. (268751), admitted Jan. 2, 1954, was a 2-year-old white boy of Puerto Rican ancestry who was admitted with a two-day history of cough, pallor, jaundice, and fever. The admitting physical examination revealed a well-developed child with a marked pallor and a slight icteric tint to his sclera. He was febrile and lethargic. There was a strange odor to his breath. The liver was 4 cm. below the right costal margin, and results of the examination were otherwise not remarkable.

On admission, the erythrocytes were 1,900,000 per cu. mm.; hemoglobin was 5.3 gm. per 100 cc.; reticulocytes were 7.9%; normoblasts were 1000 per cu. mm.; the white blood cell count was 21,000 per cu. mm., and the differential count was normal. On the second hospital day the leucocytes rose to 30,000 per cu. mm., the reticulocytes were 18%, and the normoblasts were 3000 per cu. mm. The hematocrit was 13%, and the bleeding and clotting times were normal at this time.



Naphthalene toilet-bowl deodorant.

The erythrocytes exhibited microcytosis, anisocytosis, polychromatophilia, basophilic stippling, fragmentation, and many nucleated forms on the first hospital day. These pathological forms were found until the fourth hospital day to a lesser extent. Sickling tests were repeatedly negative, as were the Coombs tests. On the third hospital day the urine reacted slightly with the guaiac test, and urobilinogen concentration was found to be normal. At this time the erythrocyte fragility was normal; bilirubin, direct-negative, indirect was 0.9 mg. per 100 cc.

The routine urinalysis was negative. The stool was negative for occult blood. The Wassermann,

Presented at the Bronx Pediatric Society, Wednesday, April 14, 1954.

Present address: New York Medical College, Flower and Fifth Avenue Hospitals.

From the Department of Pediatrics, Bronx Hospital; Joseph Lapin, M.D., Attending Physician.

* References 1-5.

† References 6-9.

‡ References 2-5.

§ Goldwater, L.; Rosenthal, R.; Luhby, A. L., and Zuelzer, W. W.: Personal communication to the authors.

cephalin flocculation, and thymol turbidity tests were normal. The electrocardiogram was normal except for a tachycardia, and x-rays for the skull, long bones, and chest revealed no pathological lesions.

The course was a febrile one initially, the temperature of 100 F becoming normal by the third hospital day. The first urine after admission was noted to be dark red. It was felt that the child had an acute hemolytic anemia due to the ingestion of some poison, the exact nature of which was not ascertained until further questioning of the parents revealed that the child had been ingesting toilet-bowl deodorant cakes (Figure), which, according to the mother, smelled like moth balls, intermittently for a period of one year. On several occasions, the child was found with as much as one-half a cake in his mouth. This, upon analysis, proved to be pure naphthalene.

The patient was placed on antibiotics and given blood transfusions, sodium bicarbonate, and ferrous sulfate. Subsequent to transfusion, the hemoglobin remained elevated at normal levels. A bone marrow examination revealed a cellular marrow with normoblastosis, indicating active erythropoiesis. After the fourth hospital day the white blood cell count, reticulocytes, and microscopic examinations of the blood smear gradually approached normal. The normoblastemia disappeared. The patient was discharged improved on the 12th hospital day.

COMMENT

This patient showed most of the typical findings of acute hemolytic reaction to naphthalene ingestion, namely, (1) positive history of naphthalene ingestion; (2) fever, lethargy, pallor, anorexia and wine-red urine; (3) severe anemia with fragmentation of red blood cells, anisocytosis, microcytosis, reticulocytosis and nucleated erythrocytes, and leucocytosis; (4) a slightly elevated bilirubin. Zuelzer states, ". . . the blood picture with the peculiar segregation of the hemoglobin into one part of the erythrocytes leaving a seemingly empty area with frayed borders, and the simultaneous presence of spherocytes are quite diagnostic."‖

Unfortunately, the dark red urine which was seen soon after admission was, by error, discarded, and the patient's subsequent urine was quite normal in color and gave a faint guiac reaction. Zuelzer and Apt found hemoglobinuria, albuminuria, pyuria, and urinary casts to be part of the initial urinary picture.[1] They also suggested that naphthalene could be found early in the blood and urine. In their four cases the RBC fragility was found increased early in the course. The severity of the reaction does not appear to depend on the amount ingested. Repeated ingestion of naphthalene (as in our patient) may produce no obviously harmful effect. However, additional ingestion may produce a severe hemolytic reaction.

The general picture resembles closely Lederer's anemia or acute hemolytic anemia of unknown origin, and it has been suggested that some cases diagnosed as Lederer's anemia may, in reality, be naphthalene poisoning.[4] Treatment consists of transfusion as needed and symptomatic management. In the presence of hemoglobinuria, alkalies have been recommended.[1]

Animal studies[1] show that naphthalene is capable of absorption and of acting as a toxic substance producing hemolytic anemia. There is evidence to suggest that it is the toxic metabolites of naphthalene, primarily alpha-naphthol, which act directly on the erythrocytes in a manner similar to a hemolytic poison such as phenyl-hydrazine.¶ Naphthalene is metabolized to a limited and variable extent by the liver. Variation in absorption and detoxification may explain differences in tolerance.

Naphthalene is found in the home commonly in the form of moth balls, and indeed, all of the cases thus far reported in this country have been due to moth-ball poisoning. It is important to realize, however, that other household substances may contain naphthalene. These include deodorants, mothproofing sprays, moth flakes, insecticides, flea powders, and some expectorants and vermifuges.[10]

SUMMARY

A case is presented of hemolytic anemia due to naphthalene ingestion in the form of a toilet-bowl deodorant.

Dr. Lawrence B. Slobody and Dr. A. Leonard Luhby gave helpful suggestions in this study.

‖ Zuelzer, W. W.: Personal communication to the authors.

¶ Part II of Reference 4.

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News and Comment

ANNOUNCEMENTS

Coming Examinations to Be Held by The American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations according to the following schedule:

New York—June 10, 11, and 12, 1955

Chicago—Oct. 7, 8, and 9, 1955

Fellowship in Pediatric Neurology.—A Fellowship in Pediatric Neurology is now available in the Children's Division of the Cook County Hospital under the auspices of the Dr. Julian D. Levinson Research Foundation. Stipend: $5000 per year. For further information, contact Dr. Abraham Levinson, at Cook County Hospital.

Standards for General Convalescent Homes Caring for Cardiac Children.—Based on a statement originally prepared by the New York Heart Assosiation, the newly issued manual of the American Heart Association, "Standards for General Convalescent Homes Caring for Cardiac Children," outlines and provides a checklist of the services, facilities, and personnel convalescent homes require if they are to meet adequately the special needs of children with rheumatic fever or congenital heart defects. Copies of the manual are available from the American Heart Association, 44 E. 23d St., New York 10, or from local Heart Associations.

Summer Camp for Diabetic Children.—A summer camp for diabetic children will be opened for the seventh season under the auspices of The Chicago Diabetes Association, Inc., from July 17 to Aug. 7, 1955, at Holiday Home, Lake Geneva, Wis.

In addition to the regular personnel of the camp, The Chicago Diabetes Association will furnish a staff of resident physicians and dieticians, trained in the care of diabetic children.

Boys and girls, ages 8 through 14 years, are eligible. For further information regarding fees, interested persons should be directed to write or phone the office of The Chicago Diabetes Association, 5 S. Wabash Ave., Chicago 3, ANdover 3-1861.

Pediatric Conference.—The University of California Medical School announces a "Pediatric Conference" from June 27 through July 1, 1955, in San Francisco. Dr. George H. Schade will be chairman of the conference, which will have as guest lecturer Dr. Charles C. Chapple, Associate Professor of Pediatrics at the University of Pennsylvania School of Medicine. Subjects to be covered will be pediatric orthopedics, developmental defects, fluid and electrolyte therapy, allergy, and care of the newborn, among others. Application for the course may be made to Dr. Stacy R. Mettier, University of California Medical Center, San Francisco 22. The fee for the course will be $65.

RARE CASE OF POLYCYSTIC DISEASE OF THE KIDNEYS

J. J. BOCIAN, M.D.
and
M. LIANG, M.D., Fresno, Calif.

POLYCYSTIC disease of the kidney is relatively uncommon in children. It is generally believed that the cysts are due to a failure of union between the secretory and collecting portions of the kidney unit. Polycystic disease of the kidney is mostly bilateral, but unilateral involvement has been reported. Bell has expressed the opinion that polycystic kidneys are inherited as a Mendelian dominant. Cairns and others list the defects with which it is most frequently associated, such as harelip, spina bifida, atresia ani, and defects of kdneys, ureters, and sex organs. Rall and Odel have found associated congenital anomalies encountered in polycystic disease of the kidneys, as polycystic liver, polycystic pancreas, polycystic spleen, cardiac defects, defects of nervous system, and defects of musculoskeletal system.

Potter classifies the polycystic kidneys found in the fetus or young infant into two groups: (1) those in which the amount of renal connective tissue is normal and (2) those in which the amount of renal connective tissue is increased. In the first group, the cysts are caused by elongation and dilatation of tubules or dilatation of Bowman's capsule. Both tubular cysts and cysts of Bowman's capsules are rather rare, and Potter had only five cases of tubular cysts among 50 cases of polycystic kidneys in Chicago Lying-In Hospital of the University of Chicago series of autopsies. Only two of the infants were born in that hospital in the course of over 70,000 deliveries. In the second group, the cysts are grossly large.

Our case is of unusual type in that the kidneys were normal in size, there were cysts of tubules and Bowman's capsules, and cystic changes of the lungs, the latter two being seen microscopically only.

Resident physician (Dr. Liang).

Department of Pathology, Valley Children's Hospital and Guidance Clinic (Dr. Bocian).

REPORT OF CASE

B. B., a white baby girl, was admitted to Valley Childen's Hospital at the age of 11 months. Her family history was noncontributory. Past history was essentially negative. Nine days before admission she developed a cough. Two days later she began having diarrhea and vomiting. She was given antibiotics by her family physician. Four days prior to admission she had a fever of 104 F. Respiration was labored. Her family physician found a few moist rales at both lung bases and made a diagnosis of bronchopneumonia. Two days before admission, she was noticed to have swelling of the eyelids. The day before she entered Valley Children's Hospital she began having convulsions and was in a comatose state. She was finally transferred from another hospital to here for further investigation.

On admission, physical examination revealed a semicomatose, febrile, pale-looking child with swelling of the eyelids and the arms. Her right fingers were twitching. Her lips and tongue were dry. Pupils were dilated and light reflex sluggish. Fundi were normal. No stiffness of neck. Lungs with scattered fine moist rales. Liver 1 cm. down. X-ray showed a bilateral pneumonitis.

Her urine persistently showed 2 or 3+ albumin and many granular casts and a rare white blood cell only on one occasion. There was mild anemia; white cell count 10,400. Spinal fluid was negative. Chemistries of blood showed nonprotein nitrogen 120, creatinine 2.6 mg. per 100 cc., serum protein 6.7 gm. per 100 cc., carbon dioxide combining power 25 vol. %, sodium 162 mEq/liter, potassium 5.1 mEq/liter. Blood pH was 7.45. Chest x-rays showed bilateral pneumonia. It was felt that the patient suffered from bronchopneumonia and renal failure due, possibly, to polycystic kidneys, based on history and urinary findings.

Autopsy Findings.—The body was that of a well-developed well-nourished, 10-month-old white girl.

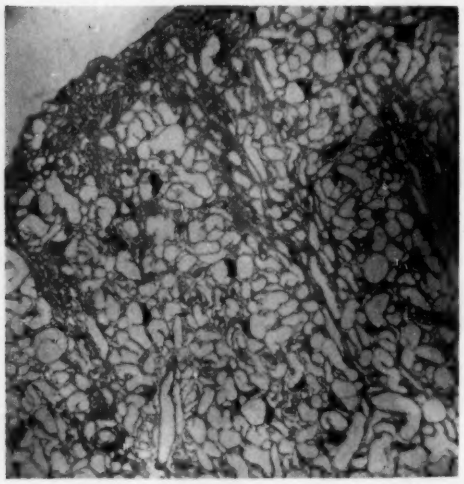

Fig. 1.—Kidney showing pronounced dilatation of Bowman's capsules and glomerular tufts attached to the walls of the cysts. Note normal glomeruli in subcapsular region. Tubules are dilated throughout; reduced approximately ½ from mag. × 100.

There were no external abnormalities. The body had already been injected with embalming fluid.

The abdominal cavity was free of fluid. The serosa was smooth and glistening. The liver and spleen were of normal size. Each diaphragm was at the level of the fifth interspace. The pleural cavities were free of fluid but the pericardial sac contained a small amount of a clear straw-colored fluid. The heart was somwhat enlarged, and both ventricles were dilated. The valves, coronaries, and vessels were normal. There was no pericarditis.

Examination of the lungs revealed the upper lobes to be crepitant and light tan. The lower lobes and right middle lobe were noncrepitant throughout, except for small portions of the anterior area. Cut sections were purple-red and quite moist. The bronchi and trachea were free. The mucosa was light tan. The liver was normal in size, shape, and consistency, and the capsule was smooth and shiny. Cut surface showed a cloudy appearance.

The spleen was normal in size and shape. Its capsule was smooth. Cut surface revealed distinct follicular markings, and the section had a dark purple-red color.

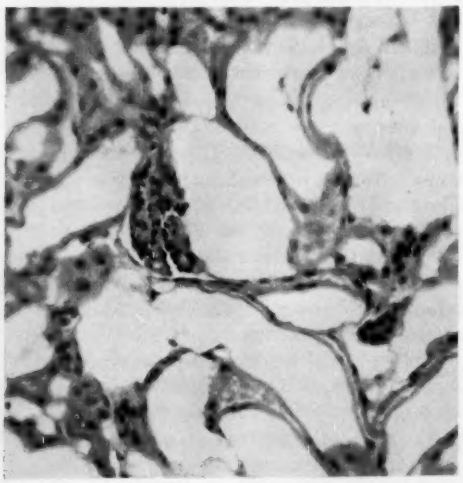

Fig. 2.—High power of Figure 1. Note compressed epithelial cells of dilated tubules; reduced approximately ½ from mag. × 440.

Fig. 3.—Cysts of lung; reduced approximately ½ from mag. × 100.

Normal adrenals and a normal pancreas were noted.

The stomach mucosa was smooth and contained several pinpoint-sized hemorrhagic areas. The lumen contained a dark fluid due to changed blood which amounted to about 4 cc. There was no colitis, and the intestines appeared normal. Both kidneys were somewhat enlarged and tense. The capsule stripped with ease, leaving a smooth reddish-tan cortical surface. There were no petechial hemorrhages. However, the surface had a slightly blotchy appearance. The corticomedullary markings were preserved. The mucosa of the pelves was smooth, grey, and glistening. The ureters were patent. Urinary bladder was essentially normal.

Examination of the brain revealed the meningeal vessels to be markedly congested. The lateral ven-

tricles were normal. The brain, on serial sectioning, showed a moderate edema.

Microscopic Findings.—Sections from each kidney revealed the glomeruli and tubules in the subcapsular areas to be essentially normal. Most of the golmeruli in the cortex, however, showed moderately to markedly dilated Bowman's spaces. The golmeruli appeared like tufts compressed in one corner, with poor differentiation of the glomerular capillaries. The adjacent tubules showed a very marked dilatation. The tubules were dilated at right angles to the surface. The epithelium in many of them was thinned out, compressed, or entirely missing. Some tubules contained casts.

Lung sections showed several areas to be present which consisted of many polymorphonuclear leucocytes infiltrating the lumina and the alveolar walls. There was a marked thinning of the alveolar walls outside these areas, with rupture of many of them. Several cystically dilated bronchi and alveolar ducts were present.

Sections of heart showed that the myocardial fibers were normal. The nuclei were small. There was no inflammation in the interstitial tissue.

Examination of brain sections showed a marked pericellular and perivascular edema.

COMMENT

Lambert, in an excellent review of the subject and by serial reconstruction of adult cystic nephrons, concludes that as yet we do not know the etiology of this disease and that the physiopathology of renal polycystic disease is different in the adult and the newborn. In the former, the cystic nephrons open into the pelvis and retain a large portion of their functional activity and participate in the formation of urine. As a result, the adult may survive to late middle age. In the infant, on the other hand, the cystic nephrons are closed systems insolated from the pelvis and do not have any function; the infant dies early in life.

Our case is of an unusual type. The kidneys were of normal size and showed no gross evidence of cyst formations, not even pinhead in size. Also, microscopically, it showed a combination of both tubular and glomerular cysts without an increase in the connective tissue.

Such a case can easily be missed if routine sections for microscopic studies are not taken.

Our case is also unusual in that polycystic kidneys are rarely the cause of death in late infancy. In 86 cases reported by Bell, only two were found from one month to one year of age. It is possible that enough normal glomeruli were present especially beneath the capsule to carry on normal renal demands but the kidneys decompensated when additional demands were made by the bronchopneumonia and diarrhea, assuming, of course, that the latter were not secondary complications.

SUMMARY

A case is presented of bilateral congenital polycystic disease of the kidneys without any gross abnormalities in an 11-month-old white girl who was perfectly well until about one week previously, when she developed bronchopneumonia. Uremia and anuria developed, and the baby died one day after admission to the hospital. The polycystic disease was of the type where there is no increase in the interstitial connective tissue.

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HYPOPLASTIC ANEMIA WITH MULTIPLE CONGENITAL ANOMALIES (FANCONI SYNDROME)

LIEUT. RAPHAEL GOLDSTEIN (MC), U. S. Army

IN THE YEAR 1927, Fanconi published three cases of a rather unusual combination of congenital defects associated with what he called at the time a pernicious-like anemia. The cases reported by him were found in three brothers of the same family. Since then a number of similar cases have been published in the European literature as well as in the literature this side of the Atlantic. Although all the cases bear a certain resemblance to each other, it is rather hard to give a precise definition to the syndrome, since there is no good explanation for its etiology, and, what is more, there seem to be a number of variations in the clinical and laboratory findings. There is, however, no doubt that the syndrome exists as a pathological entity.

In his original article, Fanconi described three siblings between the ages of 5 and 7 years with pernicious anemia but which in reality seems to have been an aplastic anemia with macrocytosis and a high color index. Associated with the anemia, he found exaggerated deep tendon reflexes, pigmentation of the skin, strabismus, and microcephaly. Zellweger, who for many years was Fanconi's collaborator, published two similar cases in 1946 and 1950. Since then other cases were reported, and definite characteristics were added to the disease. Van Leeuwen, Dacie and Gilpin, Estren, Suess, and Dameshek reported similar cases in which there was also marked dwarfism. Jimenez de Asua, Uehlinger, van Leeuwen, Hjorth, Estren, Suess, and Dameshek in theirs, reported malformations of the skeleton, particularly of the extremities. These included retarded ossification of the metacarpal nuclei, absence or malformations of the thumbs, absence of the calcaneum, congenital dislocation of the hips, and shortening of the cubitus. Hyper-reflexia was observed in the cases of Fanconi and Uehlinger. Diminished hearing was observed by Uehlinger and Estren. Heart murmurs and enlargement of the cardiac shadow on x-ray were found by Estren, Suess, Dameshek, and Jimenez de Asua. All authors found increased pigmentation of the skin in their cases. Endocrine troubles were encountered in half of the cases reported and were particularly stressed by Weil. Absence of one kidney was found in the cases of Uehlinger and van Leeuwen, whereas Dacie and Gilpin described one horseshoe kidney. Anemia was present in all cases. We may, therefore, assume that this is a syndrome characterized by hypoplastic anemia with macrocytosis and a high color index in which the following additional malformations may occur in accordance to their frequency: (1) increased skin pigmentation, (2) hypogenitalism, (3) dwarfism, (4) microcephaly, (5) anomaly of the thumbs, (6) strabismus, (7) anomalies of the ears, (8) anomaly of the kidneys, and (9) congenital heart disease. To these we may add mental retardation and sacrococcygeal sinus.

The most obvious congenital anomalies are usually noted at birth, such as club foot (Hjorth), absence of thumbs, or congenital dislocation of the hips. The anemia toward which these children are progressing usually becomes evident only in late infancy or early childhood. Frequently it becomes manifest after an infectious disease, a hemorrhage, or any state of stress which requires increased activity of the hematopoietic organs. Uehlinger is probably right when he says that the disease emerges from latency at the time when growth imposes its exigencies on a qualitatively insufficient bone marrow. Nosebleeds and bruises after relatively slight trauma are usually the first signs of thrombocytopenia. Some parents will observe pallor

and sallow skin pigmentation as the first sign of bone marrow depression. Subjectively the children feel well and adapt easily to their low blood cell counts. Only when the red cell count drops below 1,000,000 do most of these children become quiet and listless. In the cases reported here, skin infections which were reluctant to heal brought the mothers to our clinic.

Severe anemia with thrombocytopenia and leucopenia is a constant laboratory finding. Macrocytosis with hypochromia is often found. In some of the cases reported there were high reticulocyte counts, increased fragility of the red cells, elevation of the serum iron, and increased amount of bile excretion in the stools. There was hypoplasia of the bone marrow in all those cases where bone marrow aspirations were performed. Only Weil and Fanconi found occasional strands of normal bone marrow in their punctures. Van Leeuwen assumed that the bone marrow was qualitatively normal but quantitatively deficient; thus he explained that the increased demand on those strands of normal bone marrow was responsible for the presence of immature red blood cells in the peripheral smears. Some of the cases with obesity, hypogenitalism, and enlargement of the breasts in males suggested to the authors dysfunction of the hypophysis and adrenals. This was demonstrated by the workers at the Zurich Children's Hospital through abnormal insulin and epinephrine curves and an insufficient 17-ketosteroid excretion. However, only a minority of the cases showed alterations of the hypophysis or adrenal glands at autopsy. Weil obtained good results by treating his case with testicular and thymic hormones. The question may, however, be raised whether the endocrine dysfunctions reported were not secondary to the anemia. Dacie and Gilpin as well as Fanconi mention the possibility of a hemolytic factor coming into the picture of the syndrome. In their cases a hemolytic crisis was produced after a blood transfusion although the blood was well typed and cross matched. Dacie and Gilpin had one other case associated with nocturnal hemoglobinuria. They also mention having found target cells in the peripheral smear with an elevated icteric index and a positive indirect van den Bergh. There are three cases in which splenectomy was performed as a last resort, two of which seemed to have given temporary relief only, whereas the third case is still surviving.

The etiology of the disease is unknown, but there can be no question about the fact that it is familial in nature. Huber and Rohr believe that in families in which aplastic anemia occurs there is a hereditary constitutional weakness. The point that the disease is transmitted through a recessive gene is brought out by other authors, in particular Beautyman. It may well be possible that some of the cases of aplastic anemia are due to the varying expressivity of the genes for the Fanconi syndrome. Most of the authors were able to reveal isolated symptoms of the syndrome in other parts of the families, such as discrete signs of hemorrhagic diathesis and minor malformations of the skeleton, not to speak of the majority of cases which occurred in siblings. We find it hard to agree with Estren, Suess, and Dameshek, who considered that an infection during the first months of pregnancy might be at the basis of the etiology. In our case we were unfortunately unable to establish consanguinity between the parents or formes frustes in other members of the family.

The treatment of the disease is disappointing in all cases. A battery of hematonics from arsenicals to vitamin B_{12} were exhausted in clinical trial. Splenectomy seems to be a questionable procedure but remains a desperate last resort in those cases where there is evidence of hypersplenism. Only repeated blood transfusions will keep the patients alive and procrastinate the fatal outcome of the disease.

CASE 1

Present Illness.—The patient, a 4½-year-old boy, had been born after an uneventful pregnancy and normal delivery in a private hospital. Both parents are of Caucasian origin, but there is some Indian blood on the mother's side. There is no consanguinity between the parents. There are no mental or physical disorders in the family and no bleeding tendencies in the paternal or the maternal

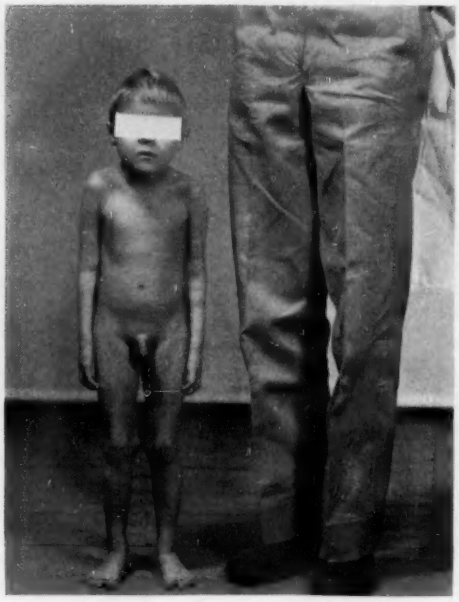

Fig. 1.—Boy 4½ years old. Weight 20 lb. (—4.3 S.D.). Height 35½ in. (—5 S.D.).

family. When the child was born, it was noticed that there was the absence of both thumbs. He apparently developed well until he was one year of age and from then on failed to gain weight. The child was toilet-trained, sat and stood alone at the normal age limit, but was never able to say but a few words, like "mommy," "daddy," "car," "hot rod." Even at present he is unable to form sentences and mostly conveys his desires by pointing at objects. He was seen by numerous private and Army doctors, but the parents were never given a definite diagnosis. The child has not been subject to any abnormal number of infections. He does not have any abnormal water intake or excretion. The child bruises very easily, and he had repeated nosebleeds during the year prior to admission. He never had black stools or hematemesis. When he was brought into the clinic, his mother's chief complaint was that the child took no nourishment but a few ounces of water or milk a day, that he constantly clung to his mother, and that he had skin infections in the popliteal spaces. Serologic tests on both parents were negative.

Physical Examination.—On admission the most striking features of this child were his small size, which made him look more like a 2-year-old than a 4-year-old, the small size of his head, the sallow pigmentation of the skin, and the absence of thumbs on either hand. The child was obviously very unhappy and refused to walk alone. EENT examination showed no abnormal signs. The oral mucosa was pale, and the teeth were well developed and in good condition. In the neck were no enlarged nodes, the thyroid was of normal size. The chest was clear to percussion and auscultation. The heartbeat was rapid and regular with a Grade III systolic murmur at the apex (this turned out to be a hemic murmur). The abdomen was soft, not tender; the spleen, not palpable, and the liver, not enlarged. The arms appeared to be rather long, and there was, as we mentioned before, the congenital absence of both thumbs; the skin was pale with a sallow pigmentation; also there were some minor skin infections in the popliteal spaces. The genitalia were normal male organs, and the testes were descended. The nervous system was normal, and there were no

Fig. 3.—Normally there should be at least five centers present at this age.

Fig. 2.—Congenital absence of thumbs.

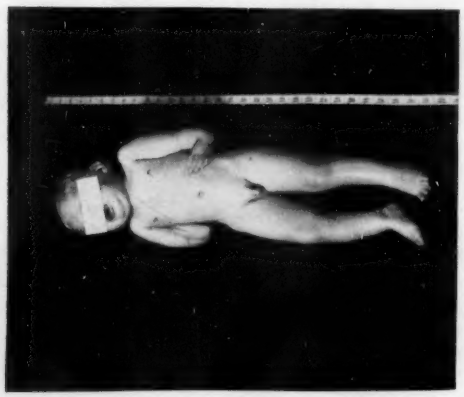

Fig. 4.—Boy 2½ years old. Weight 11 lb. (—6 S.D.). Height 25 in. (—8 S.D.).

exaggerated deep tendon reflexes; the eyegrounds were normal; head: 17½ in. (44.5 cm.) (—5 S.D.); chest: 18 in. (45.7 cm.) (—3½ S.D.); weight 20 lb. (9.1 kg.) (—4.3 S.D.); height 34½ in. (87.6 cm.) (—5 S.D.).

Laboratory Data.— WBC, 5200; neutrophiles 56, lymphocytes 36, monocytes 5, eosinophiles 3. RBC, 810,000, hemoglobin, 3.2 gm. per 100 cc. There was anisocytosis, poikilocytosis, and macrocytosis; the cells were hyperchromic. Urine: color was straw, reaction acid, specific gravity 1.007, albumin negative, sugar negative, acetone negative, 1-2 WBC per high-powered field and 0-1 RBC per high-powered field. Stool showed no ova or parasites. It was positive for occult blood. Platelet count one week after transfusion was 90,000. Hemoglobin one week after transfusion was 12.5 gm. per 100 cc. BUN. was 21. Calcium was 10.8, and phosphorus was 4.9 mg. per 100 cc. ECG showed a normal pattern with adult characteristics. Bone marrow showed the following: "Marked hypoplasia of the bone marrow involving all elements with apparent increase in lymphocytes and plasma cells, M:E ratio 2.8:1. Peripheral blood smears reveal a hyperchromic, macrocytic picture with marked variation in size and shape of the RBC's." Chest x-ray was normal; x-rays of the hands showed congenital absence of both thumbs, three bone centers in the wrists, which places this patient in the abnormal maturation group. (Normally there should be at least five centers present at this age in the average case.) Intravenous pyelogram of both kidneys showed prompt function. The renal pelvis, calyces, and ureter on the left appeared to be dilated and the ureter lengthened. The right side was poorly visualized.

Hospital Course.—The child was given a number of small transfusions until his hemoglobin came up to a respectable level. There was considerable subjective improvement. He played with amazing dexterity, giving his index fingers the function of the absent thumbs. He was the pet of the nurses and was what one would call a very good child. He certainly seemed to be a very alert child, and nothing going on in the ward would escape his attention. However, although we had no facilities for a mental evaluation, the child seemed considerably retarded for his age. Unfortunately, time element and facilities prevented us from undertaking further studies.

CASE 2

Present Illness.—The patient, a 2½-year-old boy, is the brother of the patient in Case 1, whom we examined and diagnosed as having the Fanconi syndrome. The patient was born at a university hospital after an uneventful pregnancy and normal delivery. His birth weight was 4 lb. 4 oz. (1930 gm.), and the child had to be kept in an incubator for 12 days. His weight gain after release from the hospital remained inadequate throughout. He was put under the care of the Crippled Children's Society of the area. The child first smiled at 6 weeks of age, did not stand alone when he was brought into the hospital, and first sat alone at 14 months. His appetite was good; he ate all baby foods, and got a quart of milk per day plus vitamins. The patient was not toilet-trained. He only said "daddy," "mommy," and "by by."

Physical Examination.—Markedly undersized and underweight infant; normal facial expression. EENT showed no abnormalities. Head was normal in shape; chest was normal; lungs clear to percussion and auscultation; heart regular, no murmur; abdomen soft; liver not enlarged; spleen not palpable; nervous system intact, no hyperreflexia; skin was clear, no abnormal pigmentation or pallor; marked mental retardation; extremities: deformity of both wrists in valgus position and absence of both thumbs; head 19½ in. (49.5 cm.) (normal); chest

Fig. 5.—Wrists in valgus; absence of thumbs.

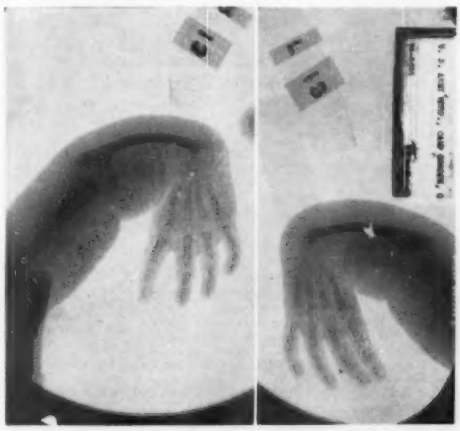

Fig. 6.—Thumbs and radii are missing.

14½ in. (36.8 cm.) (—8 S.D.); height 25 in. (63.5 cm.) (—8 S.D.); weight 11 lb. (5 kg.) (—6 S.D.).

Laboratory Data.—WBC 10,000, neutrophiles 43, lymphocytes 55, eosinophiles 1, basophiles 1, hemoglobin 11.7 gm. per 100 cc., platelets 192,000, blood morphology normal. BUN. 30.6 and 32 mg. per 100 cc. Calcium 10.4 mg. per 100 cc.; phosphorus 4.4 mg. per 100 cc. Stool for occult blood was negative. Urinalysis: color yellow, reaction acid, albumin negative, microscopic 3-5 RBC, 2-4 WBC per high-powered field. X-ray examination of the forearms showed that the radius was missing. The thumbs were missing; the wrists were about a 90-degree angle to the ulna. Chest was negative. Feet: there were extra terminal phalanges with the third and fourth toes on the right. Intravenous pyelogram was unsatisfactory and showed no concentration of the dye in the calyces or ureters. Bone marrow: moderate hypoplasia of the bone marrow apparently involving both erythrocytic and granulocytic elements with relative increase in lymphocytes. M: E ratio 3:1.

Hospital Course.—The child was very happy during the few days he stayed at this hospital. He showed amazing skill in the handling of objects, considering the severe deformity of his hands. Although no exact mental evaluation could be done at this hospital it was evident from his behavior that the child was mentally retarded. Unfortunately circumstances did not permit further laboratory investigations.

Incidence of Different Anomalies in Twenty-Seven Cases

		No. of Cases, 27	Percentage
Sex	Male	19	70.4
	Female	8	29.6
Dwarfism		11	40.7
Microcephaly		10	37.0
Skin pigmentation		22	81.5
Hypogenitalism		13	48.1
Strabismus		8	29.6
Anomaly of ears		5	18.5
Anomaly of thumbs		10	37.0
Anomaly of kidneys		6	22.2
Congenital heart		3	11.1

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Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

THE ENZYMATIC ACTIVITY OF THE DUODENAL JUICES IN INFANTS. A. CARNEVALE, G. COCOZZA, and P. DE ANGELIS, Pediatria **62**:344(May) 1954.

In vitro tests were made on the duodenal secretions of each of 7 premature, 8 newborn, and 18 older (2 to 12 months old) infants; the specimens were collected six hours after feeding on three different days. The proteolytic enzyme action was as a rule quite as high in the premature and newborn infant as in the older babies. The amylotic and lipolytic enzymatic activity were lowest in the premature infants, a little higher in the newborn, and gradually increased with the age of the baby.

HIGGINS, Boston.

SUPERIMPOSED INFECTIONS FOLLOWING TREATMENT WITH ANTIBIOTICS IN CHILDHOOD. MALTE KIENITZ and HAJO WILLENS, Monatsschr. Kinderh. **102**:472-476 (Nov.) 1954.

In two infants hospitalized because of pertussis and treated with chlortetracycline (Aureomycin), severe diarrhea and circulatory collapse developed. One of these patients died. A few days later three infants with pertussis who were on the same ward developed a rapidly fulminating pneumonia and died. Two of these infants had been treated with chlortetracycline. In two of the fatal cases Staphylococcus aureus was found in the lungs which proved to be resistant to all antibiotics except chloramphenicol (Chloromycetin). The same organism was detected in nose and throat cultures of almost every nurse on the whooping cough ward.

Enteritis and pneumonia represent the chief manifestations of superimposed infection with resistant S. aureus. In view of the increasing utilization of broad-spectrum antibiotics, superimposed infections must be expected and caution advocated in the use of all antibiotics, including the so-called older ones.

HARTENSTEIN, Syracuse, N. Y.

Metabolism; Infant Feeding; Milk and Other Foods

THE EXTRACT OF TORULAE (VITAMIN T GOETSCH) AS A GROWTH STIMULANT FOR PREMATURE INFANTS. C. POTOTSCHNIG, Minerva pediat. **6**:772 (Oct. 15) 1954.

The use of vitamin T Goetsch has seemed to the author to be superfluous as a growth stimulant for the average premature infant, as good nursing care accomplishes all that is necessary. He thinks that a growth stimulant may be helpful only when the premature infant is convalescent from an infection or is dystrophic.

HIGGINS, Boston.

MODIFICATION OF THE PARALLEL COURSE OF THE GLYCEMIC AND PYRUVICEMIC CURVES IN A GLUCOSE TOLERANCE TEST AS A RESULT OF GIVING METHANDROSTENEDIOL AND ADENOSINTRIPHOSPHORIC ACID. G. CAFFARENA and M. MERLINI, Minerva pediat. **6**:916 (Nov. 30) 1954.

Under normal conditions, the blood sugar and the blood pyruvic acid curves parallel each other. When the steroid hormone methyl androstendiol is given at the same time as the glucose feeding, the blood pyruvic acid curve does not rise with the glucose curve. This action is probably associated with the activity of the hormone in building up protein; a similar action has been reported from adenosintriphosphoric acid.

HIGGINS. Boston.

Hygiene; Growth and Nutrition; Public Health

DEVELOPMENTAL MALFORMATIONS PRODUCED BY RADIATION: A TIMETABLE OF THEIR DEVELOPMENT. SAMUEL P. HICKS, Am. J. Roentgenol. **69**:272-293 (Feb.) 1953.

Ionizing radiations will affect embryonic tissue. Differences exist in the response of embryonic tissue to radiation. The results of radiation of embryonic tissue are more dependent on the time of radiation, rather than the total dose.

There is a critical period for the formation of abnormality. The cell most susceptible to ionizing radiation is the neuroblast.

The rat and mouse embryos are relatively insensitve to radiation the first week of gestation. On about the ninth day, parts of the embryo develop radiosensitivity, and this change in susceptibility coincides with a new pattern of growth, namely, rapid differentiation and the appearance of neuroblasts. Preliminary experiments suggest that the mesenchyme and skeletal blastema may pass through a developmental stage analogous to the neuroblast.

The growth and maturation of organ systems in the rat is not a uniform progression. The differentiation of neuroblasts is spread over a longer period than that of other systems.

During the first week of gestation, in spite of radiation, no abnormalities were noted in the litters that came to term.

Radiation was administered by days, and the abnormalities produced up through the 21st day are discussed.

The experiment concludes that the neuroblast is the sensitive cell in all species tested so far—rats, mice, hamsters, guinea pigs, ducks, chickens, turkeys, and other animals—indicating that the human neuroblast is also radiosensitive. The quantitative sensitivity of the human neuroblast is not known.

HODGSON, Rochester, Minn.

GROWTH, DIFFERENTIATION, AND DISEASE. EDWARD B. D. NEUHAUSER, Am. J. Roentgenol. **69**:723-737 (May) 1953.

Growth is an increase in the size of the whole or part of a living organism, whereas differentiation implies a change of the component parts into something else. Pediatric radiology is in great part a study of the interaction of development (growth and differentiation) and disease. The impact of growth on disease may produce changes in the pattern of disease.

Many diseases are purely hereditary (marble bones, achondroplasia), many diseases are hereditary but may be altered or suppressed by environmental factors, and some environmental factors (rubella) may affect development so as to simulate genetic lesions. The role of heredity and of environment is therefore not readily apparent. Further examples of this interaction are presented.

Once a developmental abnormality has been initiated, roentgen examination may be of value in studying the effect of growth on it. The skull and some of its abnormalities are considered in detail. Study of bone contour thickness and sutural prominence enables an experienced radiologist to recognize the osseous response to brain development. Deficient cerebral development is shown by premature closure of sutures and fontanelles. Synostosis of any suture will alter skull contour if brain development proceeds normally. Cerebral aqueduct obstructive hydrocephalus results in a small posterior fossa, whereas obstruction below the fourth ventricle results in an enlarged posterior fossa.

Abnormalities of long-bone development can be studied roentgenographically, but the finding may not be diagnostic. Thus defective tubulation is observed in Pyle's disease (familial metaphyseal dysplasia), Gaucher's disease, and chronic leukemias of childhood. Radiation may produce spinal changes simulating osteochondrodystrophy.

Pediatric radiology has a great challenge for the future in the study of the pathogenesis of disease. This entails a thorough examination of the developing child in relation to his inheritance and environment.

HODGSON, Rochester, Minn.

ABSORPTION OF CARBOHYDRATE AND PROTEIN AS AFFECTED BY FEEDING CORNSTARCH, BANANA, OR GLUCOSE. LORRAINE DREISBACH and E. S. NASSET, J. Nutrition **53**:523 (Aug. 10) 1954.

Dreisbach and Nasset stated that the purpose of their investigation was to compare the simultaneous absorption of dietary protein with three different sources of dietary carbohydrate. Cornstarch was chosen to represent the carbohydrates which require hydrolysis prior to absorption and glucose to represent those that are absorbed without hydrolysis. Banana powder represents a source of carbohydrate intermediate in this respect because it requires partial hydrolysis before absorption. Each of these carbohydrates was fed as part of normal diet to rats, and the simultaneous absorption of carbohydrate and protein was observed over a period of five hours.

The carbohydrates of banana and glucose were absorbed at maximum rates in the second hour, but starch absorption did not reach maximum values until the third hour. The amount of nitrogenous material recovered from the gastrointestinal tract was always greater than

the amount of protein fed, even in the fifth hour, suggesting that the gastrointestinal tract must "turn over" somewhat more endogenous protein than is ingested. It is evident that a relatively large amount of protein must be synthesized, secreted, and recovered by the gastrointestinal tract in the process of digesting and absorbing a mixed meal. Sources of these proteins most likely are the numerous hydrolytic enzymes and mucoproteins present in the digestive juices. The superior protein-sparing effect of starch may be attributed to the fact that the carbohydrate/protein ratio in the gastrointestinal contents is consistently higher for starch than for either banana or glucose. This indicates that in the presence of starch a much larger quantity of carbohydrate is available for absorption simultaneously with protein.

FREDEEN, Kansas City, Mo.

CONGENITAL MALFORMATIONS AS RELATED TO DEFICIENCIES OF RIBOFLAVIN AND VITAMIN B_{12}, SOURCE OF PROTEIN, CALCIUM TO PHOSPHORUS RATIO AND SKELETAL PHOSPHORUS METABOLISM. ROBERT B. GRAINGER, BOYD L. O'DELL, and ALBERT G. HOGAN, J. Nutrition **54**:33 (Sept. 10) 1954.

Grainger and co-workers fed rats a diet deficient in vitamin B_{12} and riboflavin and possibly in folic acid (corn-wheat gluten rachitogenic diet—Steenbock and Black). There was a high incidence of hydrocephalus, ocular defects, and skeletal abnormalities among the offspring of dams fed this diet, and the incidence of the malformations was greatly reduced by adding the known vitamins required by the rat. The addition of these vitamins to a diet in which the dietary protein was of soybean origin gave nearly complete protection. The omission of vitamin B_{12} resulted in hydrocephalus, eye defects, and increased incidence of bone defects. The omission of riboflavin had no effect on the incidence of hydrocephalus or eye defects but increased skeletal abnormalities. The omission of both gave a still higher incidence of skeletal abnormalities. A high Ca : P ratio also increased skeletal defects. Thus it appears that a deficiency of either vitamin B_{12} or riboflavin results in defective cartilage formation and a lower phosphatase activity. Consequenlty there is a decreased rate of ossification in the skeletal tissue.

FREDEEN, Kansas City, Mo.

THE NUTRITIONAL STATUS OF PAPAGO INDIAN CHILDREN. M. G. VAVICH, A. R. KEMMERER, and J. S. HIRSCH, J. Nutrition **54**:121 (Sept. 10) 1954.

This paper reports the results of a nutritional survey on Papago Indian children. The Papago Indians were selected because they represent one of a few pure racial strains remaining in the United States; they exist on diets considered submarginal according to modern nutritional standards, and they give opportunity to determine the effects of an ample school lunch upon a population group. The 115 children were selected at random, and except for one 11-year-old child, the remainder were 12 to 16 years of age. The noon lunch for the children attending the Indian Service school was found to be ample and well balanced. For example, one luncheon consisted of Spanish rice, green beans, carrot sticks, bread and jam, milk, and canned peaches. The noon lunch from the private schools was limited and usually not well planned nutritionally. For example, lunch often consisted of bread, water, and potatoes. The blood of the children receiving the limited lunch was lower in total vitamin A and ascorbic acid than the blood of the children receiving the ample lunch. Vavich and co-workers presented data showing that a higher percentage of the former showed symptoms usually associated with vitamin A and ascorbic acid deficiencies than did the latter group. Girls from the limited school lunch showed poorer bone calcification. No significant differences between the two groups of children were found for height, weight, or age, values for hemoglobin, red cell count, white cell count, volume of packed cells, sedimentation rate, or serum riboflavin, cholesterol, glucose, or protein.

FREDEEN, Kansas City, Mo.

THE EFFECT OF FAT LEVEL OF THE DIET ON GENERAL NUTRITION: XII. THE REQUIREMENT OF ESSENTIAL FATTY ACIDS FOR PREGNANCY AND LACTATION. HARRY J. DEUEL JR., CHARLOTTE ROE MARTIN, and ROSLYN B. ALFIN-SLATER, J. Nutrition **54**:193 (Oct. 11) 1954.

Deuel and co-workers presented data showing that dietary fats are not required by the female rat for conception, for the continuance of the development of the fetuses, and for parturition. Although dietary fats or essential fatty acids are not required for the completion of intrauterine

growth, they are required for the survival of the offspring for the first critical three-day period. Up to a certain level, survival is related quantitatively to the intake of cottonseed oil or of essential fatty acids by the mother. Daily doses of cottonseed oil as low as 10 mg. insured the survival of the young for three days; in some cases, as much as 200 mg. were required per day for optimum results. The optimum daily requirement of cottonseed oil for lactation, as determined by the weight of the young at 21 days, was found to be between 100 and 200 mg. The constitutents of the fat responsible for the survival of the young and for satisfactory lactation appear to be the essential fatty acids.

FREDEEN, Kansas City, Mo.

THE EFFECT OF FAT LEVEL OF THE DIET ON GENERAL NUTRITION: XIII. THE EFFECT OF INCREASING DOSAGES OF X-IRRADIATION ON THE PROTECTIVE ACTION OF FAT ON RADIATION INJURY. AMBER L. S. CHENG, ROSLYN B. ALFIN-SLATER and HARRY J. DEUEL JR., J. Nutrition **54**:201 (Oct. 11) 1954.

Cheng and co-workers presented data which confirmed the earlier experiments in demonstrating the protective effects of dietary fat against x-irradiation in a variety of doses given at several time intervals. A simple procedure for studying the effect of diet on protection from x-irradiation involves prefeeding the weanling rats for three weeks on the test diets, followed by exposure of the animals to two 400 r doses of x-rays at intervals of four days.

FREDEEN, Kansas City, Mo.

Prematurity and Congenital Deformities

FRANCESCHETTI'S SYNDROME. C. ZUNIN and E. DE TONI, Minerva pediat. **6**:904 (Nov. 30) 1954.

Franceschetti's syndrome also goes by the names of Treacher-Collins disease and a mandibulofacial dysostosis. Patients with this condition may have all or only some of the following congenital defects.

(1) Slanting downward of the eyelids (anti-Mongoloid).

(2) Hypoplasia of the facial bones, especialy the maxilla, the zygoma, and the mandible.

(3) Malformation of the external ear, often extending to the middle and inner ear.

(4) A fistula or a groove extending from the mouth to the ear.

(5) An atypical growth of hair, which stretches down from the scalp over the cheeks.

(6) Other anomalies, as cleft palate, harelip, skeletal deformities, and heart defects.

Three cases of this syndrome in children are reported with pictures. A suggestion that the syndrome is hereditary is revealed in one case, the anti-Mongoloid eye trait being found in the father's family, and the hypoplastic mandible trait being found on the mother's side. No definite history of rubella in the mother while carrying the child could be obtained. Illustrations are used to demonstrate in the embyronic models the foci of the acquired deformities.

HIGGINS, Boston.

UNDERCOOLING OF PREMATURE INFANTS. G. JOPPICH and H. SCHAFER, Deutsche med. Wchnschr. **80**:73 (Jan. 14) 1955.

While some premature infants tolerate undercooling remarkably well, the mortality of undercooled premature infants admitted to the hospital exceeds that of premature infants admitted with normal body temperature. Of 45 undercooled premature infants, 7 died. These cases are reviewed shortly, with autopsy findings in six. Aside from usual crib coverings, no further means of heat were used. This seemed advantageous. Blocking of the ganglia of the vegetative nervous system is not necessary. The number of observations is considered too small for generalization, although in these cases the percentage of mortality was below that of premature infants before heating was omitted.

AMBERG, Rochester, Minn.

Acute Contagious Diseases

ABSENCE OF TONSILS AS A FACTOR IN THE DEVELOPMENT OF BULBAR POLIOMYELITIS. G. W. ANDERSON and J. L. RONDEAU, J. A. M. A. **155**:1123 (July 24) 1945.

Recently the proportion of cases of poliomyelitis with bulbar paralysis has supposedly increased and is greater in the older age group. One of the factors that has been suggested as significant in this localization is whether or not tonsillectomy has been performed at any time

previous to the illness. Anderson and Rondeau briefly review the findings of Top and Vaugnan (1941) and four other studies, all of which indicate that the presence or absence of tonsils at the time of attack by the poliomyelitis virus appeared to be one of the factors determining the type of response to the virus invasion. The study reported here is an attempt to confirm the observations of Top and to explore some of the causative factors.

This investigation is based on epidemiological histories gathered during the 1946 outbreak in Minnesota. In all, 2669 histories were used in the study. The authors found that persons with the bulbar type of poliomyelitis give a history of removal of the tonsils more frequently than do persons with other forms of poliomyelitis and that, if clinically recognizable poliomyelitis develops in a person who has had his tonsils removed, the likelihood of bulbar involvement is four times as great as in one whose tonsils are in situ. This higher proportion of cases of bulbar involvement in patients who have had tonsillectomy occurs at all ages regardless of the time that has elapsed since operation. This higher proportion in older persons is due primarily to absence of the tonsils rather than to age per se. The higher proporition of bulbar involvement in recent years may be due to the greater frequency of tonsillectomy and the shift in age distribution of poliomyelitis to the ages at which tonsils may have been removed. The lack of cases of bulbar involvement in certain areas may be due to the concentration of poliomyelitis in ages before tonsil removal.

Numerous hypotheses that have been advanced to explain the above findings are discussed. It is pointed out that the excess of bulbar involvement in persons who have had tonsillectomy may possibly be due to direct invasion along fibers of the 9th and 10th cranial nerves.

The data here presented do not suggest that a child who has had a tonsillectomy is any more or less likely to have a recognizable form of the disease if he is infected. They do, however, show that if a recognizable form of the disease occurs in a person who has had tonsillectomy, it is more likely to be of the bulbar type than if the person had not had his tonsils removed. The authors draw no inference as to the desirability of tonsil removal but do suggest the importance of suitable indication for removal before operation is undertaken.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE ROENTGEN STUDY OF THE CHEST IN MEASLES. JOHN DECARLO JR. and HENRY H. STARTZMAN JR. Radiology **63**:849-852, 1954.

Of 60 cases having chest roentgenograms, 43 were interpreted as showing positive pulmonary findings. Thirty-one had parenchymal infiltration; in 18 this was localized, and 13 had bronchopneumonia. Enlarged hila were present in 22 of the 43 cases. Two were negative excepting for intense pulmonary markings. Widened mediastinum and atelectasis were frequent findings. Pleuropulmonary changes were present in only two cases. Chest roentgenograms and brief histories are presented of four cases.

Mention of previous reports is made of typical measles producing identical lesions with those of giant-cell pneumonia, nuclear cytoplasmic inclusions, and other virus diseases. The extreme histopathologic resemblance of the lesions of the lung caused by virus infections seems to account for the similarity of the chest picture in all of these diseases.

ANSPACH, Riverside, Ill.

THE EFFECT OF TONSILLECTOMY ON THE MORBIDITY AND THE COURSE OF DIPHTHERIA. B. CARLETTI and D. MARRA, Minerva pediat. **6**:726 (Sept. 30) 1954.

Some data have been gathered in the city of Milan, an industrial community, as to the significance of a previous tonsillectomy on the incidence and the nature of diphtheria. Diphtheria among tonsillectomized children is less frequent, less severe, and more prone to involve the nose and the larynx. Adults and children under 6 years of age seem to get less protection against the disease by reason of a previous tonsillectomy than do the older children.

HIGGINS, Boston.

THE TREATMENT OF PERTUSSIS IN CHILDREN BY CHLORAMPHENICOL SUCCINATE GIVEN AS AN AEROSOL. A. PICCIONE, Minerva pediat. **6**:769 (Oct. 15) 1954.

Chloramphenicol succinate was used as an aerosol in a chamber in the treatment of 90 patients with pertussis. Good to excellent results are reported for 53 cases, fair results for 18 cases, and no benefit for 19.

HIGGINS, Boston.

THE IMPORTANCE OF A CYTOLOGICAL EXAMINATION IN THE DIFFERENTIAL DIAGNOSIS OF VESICULAR DERMATOSES OF CHILDREN. E. U. MIAN and L. POLI, Pediatria **62**:387 (May) 1954.

A cytological examination of a smear from a vesicle will aid in the differentiation of the herpetiform lesions (herpes simplex and zoster, varicella, Kaposi's disease) from other vesicular dermatoses (vaccinia, Tilbury-Fox dermatitis, and the aphthae of the mucous membrane). The herpetic lesions are exudative with some degenerating cells, while in the other group there is a characteristic and almost specific cellular picture. The various cytological and karyological characteristics of each type are described and illustrated.

HIGGINS, Boston.

Acute Infectious Diseases

PRIMARY VARICELLA PNEUMONIA. AMBROSE G. HAMPTON JR., A. M. A. Arch. Int. Med. **95**:137 (Jan.) 1955.

A case of primary varicella pneumonia in a 25-year-old Negro housewife is reported, and previously published cases are discussed. Most pneumonias associated with chicken pox have been previously assumed to be due to secondary bacterial invaders. The author presents evidence that his case and several others in the literature, however, represent a primary pneumonia due to the chicken-pox virus, and he feels that these illustrate a well-defined clinical entity.

JONES, Chicago.

RECENT ADVANCES IN VACCINES FOR PREVENTION OF ACUTE ANTERIOR POLIOMYELITIS. H. J. SHAUGHNESSY, Illinois M. J. **106**:20-24 (July) 1954.

In a review of studies on poliomyelitis vaccines, Shaughnessy points out that studies on animals have shown that antibodies may keep the virus from invading the blood stream and thus from penetrating the central nervous system. In this report the author confines his remarks to the work which has been done by his group with an irradiated vaccine.

Animal safety tests which available data indicate are adequate were made. Normal adult volunteers were inoculated with trivalent tissue-culture vaccine, inactivated by ultraviolet irradiation, with and without adjuvant. Antibody responses of fourfold or greater were shown by volunteers receiving adjuvant vaccine. Similar results were obtained with the aqueous vaccine. All that was demonstrated in these tests is a booster effect.

No one knows what level of antibody is necessary for solid immunity in human beings. The antibody levels produced by vaccines are far higher than those from gamma globulin. How long these higher levels of antibody persist is not known. There is no guarantee that vaccination will continue to be successful in the future.

BARBOUR, Peoria, Ill.

VENEZUELAN EQUINE ENCEPHALITIS DUE TO VACCINATION IN MAN. L. S. SUTTON and C. C. BROOKE, J. A. M. A. **155**:1473 (Aug. 21) 1954.

In 1949 a highly purified vaccine against Venezuelan equine encephalomyelitis was developed for human use. Inoculated volunteers showed excellent immunologic response. A review of the existing literature revealed that viremia had never been found after the administration of any of the three equine encephalomyelitis vaccines. The purpose of this paper is to report 14 cases of Venezuelan equine encephalomyelitis occurring in humans after inoculation with the vaccine. These 14 clinical cases were encountered in the immunization of 327 persons, who received a total of 1174 inoculations. All patients recovered.

Virus was isolated in specimens taken from 8 of 10 patients; no attempt at isolation was made in 4 cases. Although virus was recovered from only 8 of 10 persons, the authors note there is a good possibility that, had virus isolation studies been performed frequently and early enough, the agent would have been recovered from the other patients. None of the 14 persons were exposed to the virus during the course of their daily work. In seven of the eight cases virus was recovered from the blood. Viremia was detected as early as the first and as late as the fifth day of illness. The pharynx appears to be a site of predilection for this virus. Should virus not be isolated, presumptive diagnosis of the disease may be made by the demonstration of serum neutralizing antibodies. Although no attempt was made to recover the virus in the first four cases, the determination of neutralization indexes on postimmunization serums disclosed markedly

elevated titers, which, coupled with the clinical illnesses, were suggestive of the disease. The clinical aspects of the disease occurring after vaccination are briefly reviewed and compared with naturally acquired cases.

Concentrated quantities of vaccine, including samples taken from the very vials containing vaccine causing clinical illnesses, were inoculated into about 6000 animals of various species. No virus was recovered. This may indicate that by chance a clump of injective particulate matter was injected into man, or that man may be a more susceptible host for the propagation and recovery of Venezuelan equine encephalomyelitis virus.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

BLOOD AND CEREBROSPINAL FLUID LEVELS OF INTRAMUSCULAR OXYTETRACYCLINE. RICHARD KOCH, J. Pediat. **46**:44 (Jan.) 1955.

Koch's study reports five controls and eight cases of purulent meningitis. The cases of meningitis were as follows: one Hemophilus influenzae, Type B, one pneumococcus, one not determined, and five meningococcus. (One of these cases of meningococcic meningitis recovered on penicillin and sulfonamides after oxytetracycline had failed.)

Suggested intramuscular dose of oxytetracycline for susceptible organisms: 12 to 18 mg. per kilogram body weight every six to eight hours.

MACDONALD, Pittsburgh.

SALMONELLOSIS IN CHILDREN. EDWARD F. RABE, Pediatrics **13**:247 (March) 1954.

The clinical course of 12 consecutive cases of salmonellosis occurring in children from 6 weeks to 12 years of age was described. Seven of the patients presented the clinical picture of septicemia, two had bronchiolitis, two had enteritis, and one had pyelonephritis.

The limitations of the use of serum agglutination titers in diagnosing the disease were illustrated. Emphasis was placed upon the fallacy of using a narrow antigenic spectrum in conducting serum agglutination titrations, and upon the value of obtaining paired serum samples as a basis for diagnostic interpretation.

The success of antibiotics in the treatment of symptomatic salmonellosis and their failure in curing the asymptomatic intestinal carrier of Salmonella were illustrated.

FROM THE AUTHOR'S SUMMARY.

PSEUDOMONAS AERUGINOSA SEPSIS. ALBERT M. HAND, South. M. J. **47**:1049 (Nov.) 1954.

Infections due to this organism may occur in every system of the body but are more commonly found in the gastrointestinal tract, the central nervous system, and the skin. In the skin the lesions begin as small points of ecchymosis or blebs. At this time the blood culture may be positive even though the infant's temperature is normal. The skin blebs persist or enlarge and often break down, the affected skin becoming dry, dark, and necrotic. These lesions occur more commonly on the extremities and about the buttocks.

Five cases of Pseudomonas infection in infants and children aged 9 days to 7 years are reported, two of whom died. The three who recovered were treated with polymyxin B. The organisms isolated from two of the patients who recovered were resistant to penicillin, chlortetracycline, (Aureomycin), chloramphenicol, streptomycin, bacitracin, and oxytetracycline (Terramycin). Those from the third patient who recovered were sensitive in vitro to chloramphenicol and oxytetracycline, but the clinical administration of these drugs was without effect.

LOGAN, Rochester, Minn.

THE KATAYAMA SYNDROME. FRANK WALT, South African M. J. **28**:89 (Jan.) 1954.

The syndrome of fever, headache, cough, abdominal pain, enlarged liver and spleen, and marked eosinophilia is described in detail and illustrated by 12 case reports. The Katayama syndrome as described is typical of the invasive stage of schistosomiasis.

McGUIGAN, Evanston, Ill.

PREVENTION OF BOUILLAUD'S DISEASE IN CHILDREN. J. ROUVEIX, Presse méd. Supp. 19, p. 399 (March 13) 1954.

Preventive measures against Bouillaud's disease should be taken as early as the end of the initial attack. Careful attention to the rheumatic patient may shorten or reduce the relapse course by immediately resuming the treatment as soon as the initial symptoms appear. Hormonal

treatment, if early administered, seems efficacious in preventing cardiopathy. The notion of rest should prevail among the prophylactic measures. Any fatigue must be avoided during the year following the attack. Need of prolonged supervision under the best conditions of general hygiene has called for the creation of convalescence centers for rheumatic children. The routine maintenance treatment with salicylates is of little interest. Amygdalectomy is indicated for the rheumatic child, but no more than for any other case, since it proves nearly ineffective on the relapses. Contrarily, prophylactic treatments with antibiotics, sulfamides, and penicillin seem more promising.

In addition to the action on the causative infectious factor, it is also necessary to act, as far as possible, on the terrain; this is essentially based on the reaction potentiality of the defensive pituitary-adrenal system. Among those therapies able to give such a result, crenotherapy should be emphasized, as its action on the neuroendocrine balance was demonstrated by physiological experimentation.

An investigation into the condition of 52 children who had been given Bourbon-Lancy treatment after their initial attack shows the relapse rate to be 8%, as opposed to the 25% rate in untreated rheumatic cases.

FROM THE AUTHOR'S SUMMARY.

LEPTOSPIRA AND THE NERVOUS SYSTEM IN CHILDHOOD. HANS ULRICH FREYER, Ann. pædiat. **182**:271 (May) 1954.

Twenty cases of icteric leptospirosis in infancy are described. The children were examined again after a year and their spinal fluid checked, and it was found that in all, even in the so-called "benign" cases of leptospirosis, the central nervous system is invariably involved. The relatively frequent occurrence of chronic leptospirosis meningitis is pointed out, the clinical picture and the spinal fluid findings are described, and the importance of recognizing the disease is pointed out because it might be diagnosed as "neurasthenia."

FROM THE AUTHOR'S SUMMARY.

LEPTOSPIROSIS AND THE NERVOUS SYSTEM IN CHILDREN: PATHOGENESIS AND TREATMENT. HANS ULRICH FREYER, Ann. pædiat. **182**:317 (May) 1954.

With regard to the pathogenesis of leptospirosis it is stated that the signs and symptoms of the first (septicemic) stage are directly due to the effect of the organisms. For the second stage of organ manifestations, the chronic meningitis, and the late iridocyclitis the hypothesis of allergic conditions is made and arguments in favor of it are proffered.

Only in the first stage may antibiotic treatment (chlortetracycline [Aureomycin], possibly combined with quinacrine [Atabrine]) be successful. The morbid signs in the second stage cannot be prevented or influenced by antibiotics.

FROM THE AUTHOR'S SUMMARY.

INTRADERMAL VACCINATION IN THE TREATMENT OF TYPHOID INFECTIONS. D. GOTTI, Clin. pediat. **35**:753 (Oct.) 1953.

Intradermal injections of a typhoid vaccine (5 to 80 million typhoid organisms) were given every other day after the 11th day of the illness as an adjunct to chloramphenicol to 29 patients with typhoid fever. It is felt that some beneficial results were observed in 23 of the patients. Similar benefits were observed following similar treatment of 18 patients with paratyphoid fever.

HIGGINS, Boston.

THE TREATMENT OF STAPHYLOCOCCIC SEPSIS IN THE NEWBORN. G. ROTTINI and B. EVA DI GIACOMO, Lattante **25**:515 (Sept.) 1954.

The commoner staphylococcic infections of the newborn are impetigo, phemphigus, furunculosis, abscesses, and septicemia. In these conditions, the use of antibiotics should be supplemented by vaccines and antitoxins. Since strains of staphylococci are recently found to be more resistant to antibiotics, it is advisable to test the potency of the various antibiotics against the causative organism and then use the most potent.

HIGGINS, Boston

THE TREATMENT OF RHEUMATIC INFECTION WITH PARA-AMINO-SALICYLIC ACID (PAS) WITH AND WITHOUT SODIUM SALICYLATE. R. BULGARELLI and G. SARDINI, Minerva pediat. **6**:198 (March 31) 1954.

PAS was found to have a definite antirheumatic action, to lower the sedimentation rate rapidly, and to be less toxic than sodium salicylate. The giving of paraaminosalicylic acid together with sodium salicylate led in most cases to a higher and a longer-maintained salicylate level in the blood.

HIGGINS, Boston.

THREE EPIDEMICS OF INFECTIOUS HEPATITIS IN INFANTS: EPIDEMIOLOGICAL, CLINICAL, AND FUNCTIONAL ASPECTS AND BIOPSY FINDINGS. F. DE MATTEIS and G. RAGGIO, Minerva pediat. **6**:794 (Oct. 31) 1954.

In the past three winters at the Pediatric Clinic of Genoa, there have been epidemics of infectious hepatitis in infants. The mortality rate was high, being 66% in the first epidemic, 38% in the second, and 36% in the third. Extended reports of 13 cases, in infants 1 to 6 months old, from the last epidemic are presented; in this group, serial liver biopsies (needle technique) were done, 40 in all. The etiological agent was probably a virus, conveyed through nasal and fecal discharges and possibly through nipples. In several of the cases, the disease did not reach the stage of jaundice. The early symptoms were loss of weight, light-colored stools, hepatomegaly, and lack of cenesthesia. Enzymatic, flocculation, and colloidal lability tests were all found positive in the prejaundiced stage. As the jaundice appeared, the eyelids became puffy, and in one-third of the cases splenomegaly was present. Tremors and convulsions were usual terminal signs. Microscopic findings of the biopsied liver tissue showed normal-appearing nuclei, but the cytoplasm took practically no stain at all. The picture is described as being similar to that found in von Gierke's disease, but of course there were no glycogen deposits in the cells in these cases.

HIGGINS, Boston

CHLORAMPHENICOL IN TYPHOID FEVER. M. DE LA IGLESIA, Arch. pediat., Barcelona **32**:53 (July-Aug.) 1953.

The author presents 12 cases of typhoid in children, treated with chloramphenicol.

His conclusions are that the antibiotic must be continued after the fever abates, for relapses and complications may otherwise develop.

Several cases developed a leucopenia, but this disappeared when dosages were lowered. The symptomatic treatment, including nutrition, must not be neglected, especially must large amounts of vitamin B be given.

The author does not recommend the maximum dosage and warns that frequent blood cell counts must be made. All the children recovered.

ALLEN, Santa Fe, N. Mex.

NOSOLOGICAL AND CLINICAL ASPECTS OF PERUVIAN VERRUCA OR CARRION'S DISEASE IN CHILDREN. CARLOS F. KRUMDIECK, Rev. españ. pediat. **9**:625 (May-June) 1953.

The author presents clinical observations and laboratory findings in 12 children who suffered from the peruvian verruca or the more serious form, called Carrion's disease. In both types of infection the causal organism is the Bartonella bacillus, and its period of incubation (as determined by Carrion, Rosell Garcia, and others) is, on the average, 15 days. The verruca may occur as a widespread miliary type of exanthema with fairly rapid development and subsequent disappearance of the lesions, or, if there is high fever and rapid dehydration, death may occur. On autopsy the visceral organs as well as the skin may be full of the verruca so that frequently the spleen is described as a sack full of warts.

Frequently the disease is associated with other illnesses, such as malaria, tuberculosis, dysentery, typhoid, etc., and if such a concomitant disease is found, specific treatment for this helps the involution of the verruca. Otherwise, the treatment seems to be symptomatic. There is a severe anemia accompanying this disease, and it has a long period of convalescence. One attack confers immunity.

ALLEN, Santa Fe, N. Mex.

ECHINOCOCCOSIS IN CHILDREN WITH SPECIAL REFERENCE TO ITS MEDICAL AND SOCIAL ASPECTS. VELARDE PEREZ FONTANA, Arch. pediat. Uruguay **25**:173 (March) 1954.

There is a strict relationship between echinococcosis in childhood and the same in adults. Echinococcosis in childhood is characterized by the unicystic forms without complications. The percentage of multiple cysts is about the same in the child as in the adult. The frequency of echinococcosis in the child can be explained by the child's more intimate contact with dogs. Statistics show that the hydatid cyst in the child increases progressively till 14 years of age then decreases, to increase again after the age of 18, when the adult, in rural activity, comes in contact with an infected medium.

The climatological, chorographical, and age factors are very important in the extension of the hydatid diseases. Experimentation has demonstrated that the use of sodium chloride may be

an important element in the prophylaxis of echinococcosis, and its use must be advised and generalized.

Sanitary education in the schools and a law of compulsory insurance for the rural worker are indispensable to background of official prophylactic action.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF SEVERE TETANUS. WALTER MEHL, Deutsche med. Wchnschr. **79**:553 (April 2) 1954.

In a 13-year-old boy, the symptoms of tetanus developed three days after an injury, becoming rapidly severe. The treatment is given in detail. Prevention of pneumonia by antibiotics and O_2 is stressed as well as the use of curare preparations in case of attacks of suffocation, together with artificial respiration. In addition to muscle relaxing medication, Periston N may be used. Tetanus antiserum also was used, as well as tribromoethanol (Avertin). The boy recovered.

AMBERG, Rochester, Minn.

USE OF DIETHYLCARBAMAZENE IN ASCARIASIS. IDA J. VAN DIJK, Maandschr. kindergeneesk. **22**:57 (Feb.) 1954.

Van Dijk describes the treatment of two cases of ascariasis with diethylcarbamazene Carbilazine). The advantages of diethylcarbamazene, compared with other drugs used in the treatment of ascariasis, are described. According to the literature, diethylcarbamazone is nontoxic when used against Ascaris.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

RECURRENT TUBERCULOUS MENINGITIS. A. L. HOYNE, J. H. DIAMOND, and A. SCHULTZ, J. A. M. A. **155**:1234 (July 31) 1954.

The authors describe a case of tuberculous meningitis first appearing at the age of 15 in a Negro girl. She was treated with streptomycin intramuscularly for 90 days and was discharged after 119 days of hospitalization afebrile and asymptomatic. The patient was readmitted to hospital six weeks later with recurring complaints of headache, stiff neck, and vomiting. Another 90 days of streptomycin therapy intramuscularly was started. An audiogram taken after two months' therapy with streptomycin disclosed a moderate hearing loss in the high range above the range of the normal voice. Clinically the patient exhibited no difficulties in hearing. After the course of streptomycin was finished, the patient appeared clinically well and was discharged for follow-up studies.

Seven weeks later she was admitted for the third time because of headache, sleepiness, and inability to move the left arm. Studies over the next two weeks indicated a recurrence of the tuberculous meningitis, and another course of streptomycin was started intramuscularly. After 100 days of streptomycin treatment she was well clinically and was discharged.

The patient remained well, and at the end of six months a lumbar puncture disclosed fluid that was normal in all respects. At the time of the report it was nearly seven years since she first entered the hospital. She has continued to be in good health and has married and had three robust, healthy children, none of whom show any clinical evidence of tuberculous infection and all of whom have negative Mendel (Mantoux) tests.

The authors point out that this case is one of the most prolonged instances of therapy with complete recovery from tuberculous meningitis since the introduction of streptomycin. It shows that tuberculous meningitis can be cured without resort to intrathecal medication. It demonstrates that recurrences do not necessarily mean that recovery is hopeless—they mean only that treatment should again be instituted most vigorously. Finally, the fact that this patient has subsequently undergone three successive pregnancies with no breakdown of either the pulmonary or the central nervous system lesions strongly suggests that healed tuberculous meningitis need not be a contraindication to pregnancy.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

OBSERVATIONS AND RESULTS OF THE BCG. VACCINATION WITH THE SWISS VACCINE. T. BAUMANN, Schweiz. med. Wchnschr. **85**:102 (Jan. 29) 1955.

Tuberculin and BCG. were obtained from the Swiss Serum and Vaccine Institute, Bern. The vaccine contained about 8,000,000 bacilli per 0.1 ml. and was given intracutaneously with due care. The results of vaccination of infants from the newborn period to one year of age did

not differ essentially from those of the older age groups. On tuberculin testing six to eight weeks after vaccination, 99.2% of 420 infants gave a positive reaction, and in the four with a negative reaction the reaction became positive on a second vaccination. The patch test (Moro) was positive in 90%, the rest were positive to the Mantoux test. Of 1500 infants and school children up to 16 years, the six- to eight-weeks test after vaccination was negative in 1.2%. In another group of 1427 pupils 7 to 16 years of age, the reaction was negative 12 to 13 months after vaccination in only 0.07%. The tuberculin reaction in vaccinated children was considerably less intense than in spontaneously infected children. With the vaccine used, the incidence of complications was minimal. No cases of BCG. hilitis were seen.

AMBERG, Rochester, Minn.

A CHRONIC AND STATISTICAL EVALUATION OF SIXTY-THREE INFANTS, UNDER TWO YEARS OF AGE, WITH TUBERCULOSIS. B. DI GIACOMA and L. ROCCO, Minerva pediat. **6**:295 (April 30) 1954.

This report is from the Children's Hospital in Trieste. Of 42 infants with primary tuberculosis, there was only 1 death; of 6 with caseous lesions, there were 4 deaths, and of 15 with hematogenous disseminated tuberculosis, 10 deaths. The specific treatment in each of these cases was streptomycin.

HIGGINS, Boston.

ASCARIS INFESTATION OF PANCREAS IN DIABETIC COMA. R. ROCA DE VINALS and A. COMA-FABRES, Rev. españ. pediat. **10**:439-446 (May-June) 1954.

The authors report the case of a 13-year-old boy brought in in a diabetic coma. The hyperglycemia was treated, but death followed. Autopsy showed obstruction of Wirsung's duct with Ascaris lumbricoides. There was complete necrosis of the pancreas. Other organs were also affected, including a perivascular fatty degeneration of the liver.

ALLEN, Santa Fe, N. Mex.

A RARE COMPLICATION OF THE ISONIAZED TREATMENT OF A TUBERCULOUS MENINGITIS IN CHILDHOOD. E. WIESNER, Wien. klin. Wchnschr. **66**:921 (Dec. 3) 1954.

A 6-year-old girl with a confirmed tuberculous meningitis was treated with isoniazid (Rimifon) given by mouth, and streptomycin I. M. On the 81st day after the start of treatment, a very severe attack developed suddenly. Severe prostration, mutism, somnolence, pronounced pallor, circulatory weakness, severe frontal headache, vomiting, difficulty of urination, tremor, and hyperactive reflexes were associated with slight decrease of the lymphocytes in the blood. There was no rise of temperature. The incidence occurred after a total dose of 8 gm. isoniazid at time when the daily dosage had been reduced to 5 mg/kg/day. With cessation of isoniazid and administration of an antihistamine, the condition was relieved in two days. An allergic edema of the brain is assumed, with exclusion of a tuberculotoxic genesis.

AMBERG, Rochester, Minn.

Diseases of Blood, Heart and Blood Vessels, and Spleen

CONGENITAL HYPOPROTHROMBINEMIC STATES. ARMAND J. QUICK, ANTHONY V. PISCIOTTA, and CLARA V. HUSSEY, A. M. A. Arch. Int. Med. **95**:2 (Jan.) 1955.

The authors briefly review the historical background which has led to our current knowledge of the various factors which will give a prolonged one-stage prothrombin time. They describe four distinct clinical entities, all of which give a prolonged one-stage prothrombin time and all of which are congenital in origin. These are due to the following: (1) an inability to produce adequate prothrombin; (2) an altered mechanism which fixes the ratio of free to total prothrombin; (3) lack of the stable factor, and (4) lack of the labile factor. The authors discuss six families in detail which represent the first three conditions. They also give a method whereby the differential diagnosis of these states can be made. The fact that all of these states are congenital and many patients first present themselves with bleeding tendencies while still in infancy or early childhood makes it imperative that all physicians dealing with this age group familiarize themselves with the current thinking in this particular field.

JONES, Chicago.

A Case of the Wolff-Parkinson-White Syndrome in an Infant. E. Bianchi, Minerva pediat. **6**:735 (Sept. 30) 1954.

An 8-month-old girl had had several attacks of paroxysmal tachycardia. Electrocardiograms, except during these crises, showed the existence of the Wolff-Parkinson-White syndrome (a shortening of the PQ interval with a compensating lengthening of the QRS interval). There was no other cardiac pathology apparent. The interpretation of these functional disturbances may be the presence of abnormal congenital atrioventricular connections. Higgins, Boston.

The Disturbances and Risks Encountered in Cardiopneumography and Cardiac Catheterization. R. Bulgarelli, Minerva pediat. **6**:745 (Oct. 15) 1954.

This paper deals with the safety aspects rather than the diagnostic value of those procedures where a rapid intra-arterial injection of an iodine containing contrast material is given. The author's experience has been with 204 patients, 185 of them children, on whom angiocardiography was done for diagnosis of heart lesions, or angiocardiography for study of the pulmonary circulation in connection with cardiac pathology. The techniques in use at the Pediatric Clinic in Genoa are outlined. Six cases are cited where very disturbing happenings occurred from these procedures. Two children (13 and 14 months of age) had a very low blood pressure (50 mm. Hg) for three and six days following the procedure. One child (6 years old) had cardiac arrest shortly after the injection; this lasted about one minute, and then the heart beat slowly accelerated to a normal rate. One child (6 years old) 15 minutes after the injection showed a marked vasomotor reaction, with semiconsciousness, pallor, profuse sweating, tachycardia, subnormal temperature, and low blood pressure. Two children, one with a history of asthma and the other with asthmatic rales, had the typical reactions of severe anaphylactic shock; one of them had cardiac arrest for several minutes. The author's experience with aortography and cardiac catheterization is very limited. From his own experience and from reports in the literature, he regards it as much more dangerous procedure. He cites one of his own cases, where aortography was done 14 days after angiography; this child had cardiac arrest lasting some minutes.

The author has had no deaths as a result of his experience. But from his experience, he has listed the following contraindications for angiocardiography and angioneumography: 1. These procedures should not be attempted in infants under 1 year of age and only rarely in children between 1 and 2 years of age. 2. They should not be done in patients with asthmatic history, or where there is skin sensitivity to the iodine preparation. 3. A long interval should be allowed before a test is repeated. 4. It should not be attempted in a seriously ill patient or one with coronary disease or cardiac decompensation. In adults, alcoholism, plumbism, and hyperthyroidism are contraindications. Menstruation has not been found to be a contraindication.

Higgins, Boston.

The Action of the Hypophyseal Hormones on Erythropoiesis in the Normal Newborn Infant. M. Bernardi, P. Brusa and L. Piceni, Minerva pediat. **6**:781 (Oct. 31) 1954.

Frequent red blood cell counts and hemoglobin determinations were made on four groups of newborn infants until they reached the age of 60 days. One large group served as controls; a second group of 10 infants received daily for 10 days an injection of 2.5 to 5 units of an extract of the whole anterior pituitary gland; the third group of 10 infants received for 10 days daily injections of 0.25 to 1.0 units of whole posterior pituitary gland extract; the fourth group received injections of 10 to 15 units of corticotropin (ACTH) daily for four days.

The corticotropin injections were without effect on either the RBC or the Hgb. Both groups of children receiving the pituitary extracts usually showed a higher RBC, but without a corresponding increase in the Hgb. Higgins, Boston.

Electrocardiographic Study in Children (Not Cardiac Patients) Following Angioneumography. R. Bulgarelli and F. Abbo, Minerva pediat. **6**:790 (Oct. 31) 1954.

Electrocardiographic records were made on 19 children, none of them cardiac patients, before, during, and at various intervals after the rapid intravenous injection of 20 to 40 cc. of an Ioduron solution. After a study of these records, the conclusion was reached that angiopneumography will rarely if ever affect the function of the normal heart. Quoting from his own experience, the author feels that the effects of such injections in children with cardiac decompensation are not good and are risky; in cases of compensated cardiac lesions, some caution is necessary.

Higgins, Boston.

Diseases of Nose, Throat, and Ear

SOME FACTORS IN THE INTELLIGIBILITY OF CLEFT-PALATE SPEECH. BETTY JANE MCWILLIAMS, J. Speech & Hearing Disorders **19**:524-527 (Dec.) 1954.

Forty-eight cleft-plate patients between the ages of 17 and 59 years recorded on tape one of 12 lists of words, phrases, and short sentences in such a way as to include the 23 major consonant sounds in proportions comparable to the appearance of these sounds in conversation. In addition, each subject also recorded a short prose passage. Consonant articulation errors are correlated closely with nasality ratings. Nasality ratings depend to a large extent upon the intelligibility scores. The importance of velar-pharyngeal closure as a first step in therapy may have been overemphasized.

PALMER, Wichita, Kan.

CONGENITAL DISORDERS OF THE LARYNX. DANIEL C. BAKER JR., New York J. Med. **54**:2458 (Sept. 1) 1954.

Baker is a surgeon on the E. N. T. Staff of the Columbia University Medical Center. He states that congenital disorders of the larynx "are not unusual." The diagnosis is easy, but the problems therewith may be formidable. They may be classified as stridor, cysts, webs, paralyses, stenosis, angiomas, and tumors. The symptoms are obstructive dyspnea, hoarseness, stridor, weak or absent sounds, and dysphagia. At birth, the glottis chink measures 7 by 4 mm. Narrowing of this chink causes most of the symptoms. Inability to cry is common. The little patient who cannot breathe properly presents a feeding problem: He will refuse all nourishment because he cannot breathe and swallow simultaneously. Stridor is usually inspirational, but may be expirational at times. Pressure on the trachea may be due to anomalies of the aorta or esophagus; therefore, examination by x-ray is the rule in all cases. Stridor usually disappears after the first year, but a congenital vascular ring requires surgery. Webs, next in frequency to stridor, occurred in 11 patients over a period of 20 years' experience; they were found at the anterior commissure, usually. The ventricular bands may be involved occasionally. Voice disturbance was the commonest symptom, either weakness or no voice, and no crying, but with obstructive dyspnea. The web must be incised and the larynx dilated. But recurrence is common, and thyrotomy with complete excision, with insertion of a "tantalum keel," may be necessary. Congenital cysts cause hoarseness and obstruction. Surgery is imperative, and the results are good.

Congenital paralysis of the cords is unusual, but may occur from central hemorrhage, and is commonly bilateral. When the paralysis is unilateral, some cardiovascular anomaly is likely. Congenital stenosis has been reported by Tucker, Glaser, Landau, and Heatley. O'Kane (G. H.) reported a case in the *Laryngoscope* for July, 1936. Obstruction was subglottic, and one could not get through with a 3-mm. bronchoscope. Some three or four operations for removal of recurring scars were performed, followed by dilatation. The voice obtained as a result was "fair," and the patient was successful in college in making herself understood.

Other congenital conditions of less significance occur, namely, angiomas, cystic hygroma, tracheoesophageal fistulas, "autonomic reflexes," etc. Hemangiomas occur now and then and are difficult to deal with.

The laryngologist has a great responsibility when confronted by these conditions. It is expected that the obstetrician will be the first to discover such lesions. In any case, the main objective is to secure good respiration and a satisfactory voice. External surgery may do harm if it alters the intrinsic structures: blood vessels and nerves. Cicatricial change or persistent swelling may defeat the purpose. The growth centers in the larynx may be stunted by whatever procedure, with resultant defect in development and laryngeal function. Eighteen references to the literature make this essay a complete and exhaustive study of a field in which relatively few laryngologists have a wide experience.

I. W. VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

METHODS FOR DETECTING AUDITORY DEFECTS IN THE YOUNG: FIVE MINUTE "ALERT." EDMUND PRINCE FOWLER SR., New York J. Med. **54**:3095 (Nov. 15) 1954.

Fowler is Chairman of the Subcommittee on the Hard of Hearing and Deaf of the Medical Society of the State of New York. This paper was read at the Annual Meeting, Pediatrics Section, May 14, 1954. Hearing tests for school children are fundamental to the child's further education, but only "supplemental" in testing the infant. Elaborate tests with expensive machines

require special training of the examiner. They are often unnecessary or overemphasized. The degree and pattern of deafness are, of course, basic to further management. It may be difficult to measure hearing in a child below the age of 5, but by making it a sort of game, a test may become fairly accurate. "Children with no defect in hearing . . . have a 10% to 15% greater hearing capacity than adults. This fact is commonly forgotten." We must rely upon the acuity of observation in parents of children who are of preschool age. Environment is the principal factor. A child playing in a room adjacent to his elders may be so intent upon play that he does not answer a question or command, but he is not so often deaf as inattentive. Nearness or farness may be determinative of hearing degrees. If he does not hear a passing fire engine or automobile, a church bell or barking dog, there is a suspicion of deafness if inattention can be discounted. It is important to know whether the deafness is irreversible; if so, it is well to send the child to a nursery school for the deaf at 2½ years or before 3 years.

I. W. Voorhees, New York [A. M. A. Arch. Otolaryng.].

Discussion: Congenital Deafness. A. A. J. van Egmond and Others, Proc. Roy. Soc. Med. **47**:937 (Nov.) 1954.

Congenital deafness is a partial or complete loss of hearing transmitted through heredity or caused by environmental influences during prenatal life and leading to mutism. Two groups are mentioned: (*a*) Dominant inner-ear deafness, which develops usually at middle age. It is congenital only in the sense of being one of the six characteristics of the hereditary syndrome first described in 1951 by Waardenburg. (*b*) Sporadic recessive deafness. In dominant hereditary deafness, development of the bony cochlea becomes arrested, with malformations in the soft cochlea, with an intact acoustic nervous system. But in recessive sporadic deafness, all soft parts are affected, i. e., nerve trunks and fibers, central nuclei, and tracts with the cochlear bone intact. In each group Corti's organ is damaged, with, therefore, varying degrees of deafness. Congenital atresia auris causes congenital deafness if it is bilateral. A hereditary element is possible, but damage in utero is likely. Anatomical irregularities are confined chiefly to the middle ear, and so the deafness is conductive and may be improved by fenestration. Erythroblastosis fetalis may also cause congenital deafness. After birth, icterus gravis may supervene and kernicterus may appear. Such lesions may appear in the nuclear pathways, giving rise to severe perceptive deafness. Environmental factors are found during the 8 to 12 weeks of pregnancy while organs and systems are forming, and cells still undifferentiated are highly vulnerable. Virus infections may cause both deafness and cataracts. Syphilis is a well-known cause of congenital deafness, but may appear at the 8- to 12-year age period. Diagnosis of congenital deafness depends chiefly on history as stated by the parents.

Rubella is a cause of severe deafness. While the bony labyrinth may be normal, Reissner's membrane may be collapsed and adherent to Corti's organ. The striae vasculares are damaged or "almost absent." There are changes in the tectorial membrane, but cells of the apiral ganglion and the nerve fibers are seldom, if at all, affected. The general discussion brought out the fact that rubella in the first trimester of pregnancy produces grave changes in the fetus, especially in the endolymph, utricle, and saccule, and incomplete development of Corti's organ. Collapse of the saccule may have occurred during the mother's attack by rubella. Hemolytic diseases in the newborn infant based on clinical and pathological observations were discussed. Some 30 cases were reviewed, which fell into two groups: one with a fairly moderate loss of high frequencies, the other with a severe loss of high frequencies. Emphasis was laid on the neurological findings in relation to congenital deafness. It is easy, he said, to interpret dullness or mental deficiency in these children when, in fact, they may be mentally normal! All children who survive hemolytic disasters must be tested thoroughly to determine the kind and degree of deafness and what can be done to improve the hearing.

I. W. Voorhees, New York [Condensed from A. M. A. Arch. Otolaryng.].

Diseases of Lungs, Pleura, and Mediastinum

Effect of High Concentrations of Carbon Dioxide and Oxygen on the Respiration of Fullterm Infants. Herbert C. Miller, Pediatrics **14**:104 (Aug.) 1954.

Five per cent carbon dioxide added to 20% oxygen is a more powerful stimulus to respiration of healthy full-term infants than is 100% oxygen. Full-term infants hypoventilating as a result of exposure to low concentrations of oxygen had their minute volumes restored more

rapidly and to a greater extent when 5% carbon dioxide was added to oxygen concentrations varying from 12% to 95% than when 100% oxygen was administered.

The age of the infant appeared to have but slight effect on the response made to breathing 5% carbon dioxide or 100% oxygen. Infants under 2 or 3 hours of age were not tested.

The value of adding carbon dioxide to air or oxygen in the treatment of "asphyxia neonatorum" has been discussed. Too little is known concerning the chemical, physiologic, and anatomic changes occurring in this loosely termed condition or even in healthy newborn infants to warrant a pessimistic attitude towards the use of 5% carbon dioxide added to air or oxygen in the treatment of newborn infants with respiratory insufficiency.

FROM THE AUTHOR'S SUMMARY.

PULMONARY ATELECTASIS IN YOUNG CHILDREN. MARGARET I. GRIFFITHS, Arch. Dis. Childhood **28**:170 (June) 1953.

Seventy-seven children, aged 5 years or under, suffering from lobar or segmented atelectasis were studied. The children were followed as inpatients or outpatients until reaeration had taken place or bronchiectasis had been confirmed.

In the majority of cases, reaeration took place within six months.

The diseases predisposing to atelectasis fell into six main groups: acute infective atelectasis, primary tuberculosis, pneumonia, asthma, pertussis, and upper respiratory infection.

In this series, eleven children developed bronchiectasis in fifteen lobes.

KELLY, Milwaukee.

ENTEROGENOUS CYST OF MEDIASTINUM. T. A. SALE, Arch. Dis. Childhood **28**:325 (Aug.) 1953.

A case is reported of a 3-month-old baby in whom a cyst, lined by intestinal mucosa, was removed from the mediastinum by operation. Convalescence was complicated by a chylothorax, which was cured by a simple aspiration. The features and the literature of mediastinal gastro-enterogenous cysts are reviewed.

KELLY, Milwaukee.

SEROLOGIC TESTS IN INTERSTITIAL PNEUMOCYSTIC PNEUMONIA IN THE INFANT. B. NAVRATIL, Z. SMID, and K. BARTA, Ann. paediat. **183**:63 (July) 1954.

It has been found that the serological reaction and the complement fixation test are valuable laboratory methods in order to ascertain and confirm the clinical diagnosis of pneumocystic pneumonia. In 66 infants, treated in the Children's Hospital of the Palacky University of Olomouc, 55, i. e. 83.3%, showed a positive serological reaction. Still better results are to be expected when this method has been perfected.

FROM THE AUTHORS' SUMMARY.

ETIOLOGICAL OBSERVATIONS IN THE INTERSTITIAL PNEUMONIA OF EARLY CHILDHOOD. G. A. VON HARNACK, Ann. pædiat. **183**:224 (Oct.) 1954.

An increase in the incidence of interstitial pneumonia of early infancy has been observed in Hamburg during 1950-1954; 191 cases are reviewed, 42% with a birth weight of 2500 gm. and more.

The peak of the morbidity occurs during the third and fourth months. The earliest case began in the fifth week, the latest in the seventh month. The greater the birth weight, the smaller is the average gain until the beginning of the illness, which points to previous damage, particularly in the mature children.

The incubation period varies between 1 and 2 months: the extremes being between 22 and 78 days. The cases observed in their homes allowed conclusions regarding the risk of infection. Observations made on 15 pairs of twins show that the smaller partner is not always the one in greater danger. Occasionally babies born at home became infected with interstitial pneumonia without known contact. When admitted to baby wards they are responsible for a further spread of infection. The most important cause for the spread of the disease is the transfer of babies during the incubation period from hospital to hospital, from hospital to their homes, and vice versa. The infectiosity begins already during the incubation period. Infection seems to be possible by indirect contact.

No reliable therapeutic agent exists: there may be a slight superiority of Cyren B and cortisone. In case of superinfection with pyogenic organisms antibiotics are indicated. The mortality in our cases was 39.9%. The relatively best prognosis appears to be in children with a birth weight of 2000 to 2500 gm. FROM THE AUTHOR'S SUMMARY.

HILAR ADENOPATHY IN CHILDHOOD. SERGIO TORI, Riv. clin. pediat. **54**:1 (July) 1954.

The author, after having made mention of anatomic lymphatic cervical-thoracic connections and of the complex etiophathogenesis of hilar adenopathy, examined 200 cases of girls who were received in a nursing home intended for the struggle against tuberculosis; girls were suffering from hilar adenopathy, and the author points out that 25% of the above cases were not of the specific kind of hilar adenopathy. According to some specific clinic laboratory data, he places these cases under the categories of the simple nonspecific hilar adenopathy and he explains their etiopathogenetic mechanism through some recidivist phlogistic oropharyngeal action.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL CYSTIC MALFORMATIONS OF THE LUNG. E. SANCHEZ VILLARES and A. LOPEZ BERGES, Acta pediat. espan. **12**:783-812 (Sept.) 1954.

This is the first part of a study the authors are making on cystic malformations of the lungs in infants.

There is an extensive review of literature and discussion of the 18 or more names which have been applied to this condition. The cystic disease of the lung must not be confused with blebs or bullous emphysema. The latter are acquired while the cystic malformations are congenital. The cysts have a well-defined wall with epithelial lining, which is not true of blebs.

The authors present four case histories with x-ray studies and pathological studies on the one case which came to autopsy. Symptoms, diagnosis, and treatment are discussed.

Theories as to the causes and the embryology and pathology described. Agenesis of the lungs may be a cause. This would begin in the first or second month of gestation and results in pulmonic unilateral agenesis.. In later months there may be early dysgenesis and late dysgenesis which result in various degrees and type of malformations. ALLEN, Santa Fe, N. Mex.

BRONCHOSCOPY IN BRONCHIAL GLAND PERFORATION. EMILIO ALEMAN, J. M. ROUCO, and E. RIVERO, Arch. med. inf. **23**:222 (July, Aug., and Sept.) 1954.

We have made a correlated study of the roentgenological, bronchographic, and bronchoscopic data in 15 cases showing perforation of a caseous lymph node into the bronchial lumen as a complication of childhood type tuberculosis found among 60 cases of pulmonary consolidation in children from 0 to 5 years of age.

There were abnormalities in 12 of the 15 cases, developed as consequence of the bronchial wall alterations determined by the fistula itself. The pathological aspects were distributed as follows:

Complete stenosis of a bronchus—5 cases
Partial stenosis of a bronchus—2 cases
Widespread bronchial dilatations—1 case
Slight bronchiectasis—2 cases
Bronchiectasis plus agglutination—2 cases

FROM THE AUTHORS' SUMMARY.

MALFORMATION OF HUMAN LUNG AND POSSIBILITY OF SURGICAL TREATMENT. H. BRUCK, Wien. klin. Wchnschr. **65**:241 (April 17) 1953.

A classification of the various forms of malformation of the lungs is given. The possibility or necessity of surgical intervention is discussed. AMBERG, Rochester, Minn.

Nervous Diseases

ASSOCIATION OF MATERNAL AND FETAL FACTORS WITH THE DEVELOPMENT OF EPILEPSY. A. M. LILIENFELD and B. PASAMANICK, J. A. M. A. **155**:719 (June 19) 1954.

The prenatal and paranatal records of 564 epileptic children born in Baltimore between 1935 and 1952 showed significantly more complications of pregnancy and delivery, prematurity, and abnormal neonatal conditions than a similar number of matched controls. These abnormalities

were just as frequent among epileptic children whose parents did or did not have epilepsy. These epidemiological findings throw some light on the etiology of epilepsy and raise doubts as to the genetic basis of convulsive disorders.

The pattern of factors such as complications of pregnancy, prematurity, and neonatal abnormalities that appear to be associated with epilepsy is similar to that previously found to be associated with cerebral palsy, stillbirths, and neonatal deaths. In a previous paper by Lilienfeld and associates, it was postulated that there exists a continuum of reproduction casualty composed of a lethal component consisting of stillbirths and neonatal deaths and a sublethal component consisting of cerebral palsy. The results of the present study suggest that this sublethal component should also include epilepsy. This observation, together with the fact that approximately one-third of persons with cerebral palsy have convulsive seizures, suggests that cerebral palsy may be a result of a severer type of brain damage than is epilepsy. The results are sufficiently suggestive to warrant the continuance of similar studies concerning other possible components of this continuum. They also warrant giving serious consideration to the possibilities of establishing concurrent studies in which a group of infants classified by these maternal and fetal factors could be followed, so that one can actually measure the risks of various neurological conditions associated with these maternal and fetal factors developing.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Psychology and Psychiatry

GROUP DISCUSSIONS WITH PARENTS OF ILL CHILDREN. LUIGI LUZZATTI and BARBARA DITTMANN, Pediatrics **13**:269 (March) 1954.

Group discussions with parents of diabetic children were started as part of the services offered in the metabolic clinic of the Children's Hospital of the East Bay, followed later by similar groups of parents of children with cerebral palsy. This approach to some of the delicate problems confronting parents of children with chronic disease and the children themselves was utilized in an attempt to solve some of the aspects of care that cannot be dealt with entirely in a one-to-one approach in a clinic or doctor's office. The technical aspects of such groups are presented, and some of the significant points are discussed.

FROM THE AUTHORS' SUMMARY.

Diseases of Genitourinary Tract

THE RESPONSE OF IDIOPATHIC RENAL ACIDOSIS TO ORAL SODIUM LACTATE. THOMAS STAPLETON, Acta pædiat. **43**:49 (Jan.) 1954.

A case of idiopathic renal acidosis with coincident hypoelectrolytemia and hypercalcemia is described. The renal response to the administration of sodium lactate is examined, and it is shown that the over-all response is similar to that which would occur in a normal child. The prolonged administration of sodium lactate did not cause a depletion of potassium. The findings are consistent with the hypothesis that the underlying defect is a failure on the part of the kidney to regulate the excretion of bicarbonate.

FROM THE AUTHOR'S SUMMARY.

IDIOPATHIC RENAL ACIDOSIS. LARS H. GABRIELSEN, Acta pædiat. **43**:198 (March) 1954.

A case of chronic acidosis diagnosed at the age of 4 months and followed for two years is discussed. The biochemical changes in the blood and urine were similar to those described in idiopathic renal acidosis. Calcifications in the renal parenchyma were first demonstrated by roentgen examination at the age of 2 years. There was no etiological explanation for the patient's condition, which, being apparent from the first months of life, appeared to be congenital. Alkali treatment had a beneficial effect on the symptomatology but no curative effect upon the acidosis.

FROM THE AUTHOR'S SUMMARY.

Diseases of Eye

THE FUNDUS OF THE EYE AND HYDROZIDE OF ISONICOTINIC ACID. L. DOLCET, Acta pediát. españ. **11**:67 (Jan.) 1954.

The author comments in the remarkable efficacy of isoniazid on the involution of lesions in the eye, especially the fundus and the extrinsic muscles, following its use in patients with tuberculous meningitis.

ALLEN, Santa Fe, N. Mex.

TREATMENT OF STRABISMUS IN CHILDHOOD. RAUL RODRIGUEZ BARRIOS, JUAN V. ECHAGUE VERA, and ROBERTO VAZQUEZ BARRIERE, Arch. pediat. Uruguay **25**:388 (June) 1954.

The treatment of strabismus in childhood tends toward the ideal of a motor and functional correction, which is not always possible, especially when treatment has been started late. In the child less than 10 years old, the treatment is carried out in several stages. Two of these are (1) to correct the refraction with permanent use of glasses, (2) to treat the amblyopia by a permanent occlusion of the normal eye; the age of the patient being very important and how early it began, prolonging it until the best possible vision is obtained and until the orthoptic treatment can be begun, if possible. It will be done when the child has the mental age to cooperate.

When an angle for distance remains in spite of the treatment, it is necessary to operate. If the child is too small for orthoptic treatment, it must be operated from 2 years of age on; if it is older and the treatment is possible, it is ideal to obtain normal correspondence and fusion, as preoperative treatment.

We carry out the surgical correction of strabismus (1) when after wearing glasses permanently for more than three months, an angle of deviation persists and the child is too small for orthoptic treatment; (2) when it has been possible to do these exercises without change in the angle of strabismus; (3) in cases of angles larger than 20 degrees for distance; (4) if there is irreducible amblyopia, we prefer to wait until the age of 12 to 15 years. In most cases, we use general anesthesia. In the first operation, we prefer to work on the nonfixing eye and the one that has the worst vision. When there is a very big angle, it is sensible to operate first on one eye, because the operations done on several muscles at a time can give overcorrections.

FROM THE AUTHORS' SUMMARY.

Cutaneous Diseases; Allergy

STUDIES ON FACTORS INFLUENCING RAGWEED POLLEN COUNTS IN THE NEW YORK METROPOLITAN DISTRICT: I. POLLEN STUDIES ON AMBROSE LIGHTSHIP IN NEW YORK HARBOR. RICHARD D. WISEMAN, S. SENIOR SACK, BERNARD B. SIEGEL, ISRAEL GLAZER, and MATTHEW WALZER, J. Allergy **25**:1 (Jan.) 1954.

The purpose of the study was to show the effect of wind, wind direction, and wind velocity on the pollen count. The study was done in 1949 and 1950.

There were 10 locations in metropolitan New York where slides were placed, one of which was Ambrose Lightship, located nine miles from the nearest land; here the absence of ragweed was complete.

The Durham Shelter and the technique recommended by the Pollen Survey Committee of the Research Council of the American Academy of Allergy were used.

Ragweed pollen was found in considerable amounts on the slides exposed on Ambrose Lightship.

Wind direction and wind velocity determined the amount of pollen found on the slides on the Lightship. The counts were greater when the winds came from the west and southwest, and the velocity was highest. The greatest concentration of ragweed is to the west and southwest of Ambrose Lightship.

The authors state: "An elimination program designed to free the city (New York) of ragweed pollen will only be completely successful when ragweed plants are completely and permanently eradicated from wide areas in every direction from which winds may carry pollen into the city."

HOYER, Cincinnati.

LATENT ATOPY AND THE INCIDENCE OF THE ATOPIC STATE. SHEPPARD SIEGEL and THOMAS SEIDMAN, J. Allergy **25**:20 (Jan.) 1954.

Two hundred twenty-seven persons admitted to the surgical wards of a general hospital for conditions not known to have any relation to atopy were tested intracutaneously with pollen and dander extracts and interrogated as to the occurrence of clinical manifestations of atopy.

The latent or subclinical phase of atopy as indicated by reactions to intracutaneous testing in the absence of past or present allergic symptoms was observed in 15 subjects, or 6.6%. Atopy in its clinically manifest phase was found in 32 subjects, or 14.1%, making a total incidence of 47, or 20.7%.

Accordingly, from this study it would appear that the total incidence of atopy in the general population is about 20%, two-thirds being in the clinical phase and one-third in the latent phase.

Five subjects with latent atopy were tested by the passive transfer method. In only one case was this positive, in four others, negative. It is suggested that in the latent phase of atopy circulating reagins may not usually be present in sufficient titer to permit a positive transfer reaction despite the presence of repeated strong reactions on direct skin testing.

HOYER, Cincinnati.

ERYTHEMA MULTIFORME EXUDATIVUM TREATED WITH CORTISONE OR ADRENOCORTICOTROPIC HORMONE. V. T. WEEKS and W. X. LEHMANN, J. Pediat. **44**:508 (May) 1954.

The authors report four cases of erythema multiforme exudativum (Stevens-Johnson syndrome) in children. This clinical entity is characterized by any type of erythematous rash from the iris to the bullous type and may involve any of the mucous membranes of the body: severe stomatitis, conjunctivitis, bronchitis or bronchopneumonia, balanitis, urethritis, vulvovaginitis, and, rarely, acute gastroenteritis or endocarditis. It is accompanied by severe constitutional reactions which include hyperpyrexia, marked toxicity and prostration, and often generalized edema.

The studies show that corticotropin (ACTH) or cortisone is the treatment of choice in erythema multiforme exudativum.

MACDONALD, Pittsburgh.

PRIMARY ALLERGIC REACTIONS FOLLOWING INJECTION OF ANTITETANIC SERUM IN MEMBERS OF ONE FAMILY. H. J. VAN MAANEN and W. J. QUARLES VAN UFFORD, Nederl. tijdschr. geneesk. **97**:524 (Feb. 28) 1953.

Two members of a family showed direct (atopic) serum reactions following the first injection of antitetanic serum. Several siblings showed a positive skin reaction to horse serum. The necessity of cutaneous tests is pointed out. In this instance there existed only mild allergic reactions (to acetylsalicylic acid, jellyfish, and strawberries) in the family. In the second case under discussion (a type of serum disease), a tetanoid clinical picture developed.

Measures to be taken in order to prevent injection of serum in case of an accident by a surgeon unaware of the patient's hypersensitivity are discussed.

VAN CREVELD, Amsterdam.

Miscellaneous

ARE HOME ACCIDENTS IN CHILDREN PREVENTABLE? STUDY OF FOUR HUNDRED NINETY-ONE CASES. JAMES M. DENNIS and ALBERT D. KAISER, Pediatrics **13**:568 (June) 1954.

A series of 491 nonfatal home accidents involving children, occurring in a 10-month period in the city of Rochester, N. Y., is presented. These accidents were obtained from hospital emergency rooms and investigated by the author and public health nurses. Of these 491 cases, 284, or 58%, were judged to be preventable. Reasonable supervision by an adult and the use of ordinary precautions against accidents were outstanding as means of prevention. The statistically typical accident involved a boy under the age of 5 years who was playing in the porch and yard in the afternoon and fell from a height and cut his head. No mechanical factors were involved, and an adult was at fault. Methods of prevention of accidents are discussed.

FROM THE AUTHORS' SUMMARY.

EXPERIENCES WITH A. C. T. H. AND CORTISONE. CONSTANCE C. FORSYTH, Great Ormond St. J. (No. 6) p. 85, Dec., 1954.

Use of corticotropin (ACTH) and cortisone was found to be of doubtful value in rheumatic fever, though more encouraging in Still's disease and some of the collagen diseases. There was some beneficial effect in acute leukemia, hemolytic anemia, and one case of erythrogensis imperfecta. A case of Addison's disease responded dramatically. In most cases, withdrawal of the drug presented a major difficulty because of the tendency to relapse.

MCGUIGAN, Evanston, Ill.

KEROSENE POISONING. G. COELHO, Indian J. Child Health **2**:161 (April) 1953.

The old problem of kerosene poisoning is again emphasized. Caution is urged in lavaging the stomach, as it increases the danger of aspiration. Unless a good volume of oil is known to have been swallowed, lavage should be withheld. Because of the danger of pulmonary edema, treatment should include penicillin, oxygen, and intravenous dextrose.

McGUIGAN, Evanston, Ill.

THE POSSIBILITY OF ORAL SUBSTITUTION THERAPY WITH LIVING ESCHERICHIA COLI WITH MAINTENANCE OF THEIR FUNCTIONAL CAPACITY. F. A. PEZOLD and H. TSCHECH, Deutsche med. Wchnschr. **79**:961 (June 11) 1954.

Escherichia coli, being resistant to streptomycin, were tested with pepsin mixtures and stomach juice of various acidity. Cultures were administered by mouth with a hyperacid stomach juice. More than 20 minutes was necessary to inhibit growths. The resistant bacteria could be cultured from the stools on an average for a period of five to six days after one oral administration.

AMBERG, Rochester, Minn.

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in Detroit, on April 1, 2, and 3, 1955.

Adams, Ellis Wentworth, Jackson, Mich.
Allen, Richard, Aberdeen, Md.
Anderson, William Blair, Philadelphia.
Bailit, Irving William, Needham, Mass.
Baird, Henry Welles, III, Haverford, Pa.
Baldwin, DeWitt C., Jr., Seattle.
Barber, Donn Richard, Denver.
Barron, Stanton J., Jr., Rapid City, S. Dak.
Berry, Ralph H., Jr., Reading, Pa.
Bickel, J. Edmund, Owensboro, Ky.
Binns, Veronica B., Brownsville, Pa.
Blood, Mary Josephine, Wichita, Kan.
Bloomfield, Richard Alan, Shaker Heights, Ohio.
Bond, Donald Buckey, Clayton, Mo.
Champlin, Gardner, Pueblo, Colo.
Cheek, Donald Brook, Cincinnati.
Clark, William M., Jr., Portland, Ore.
Cooper, Marvin E., Lincolnwood, Ill.
Corbett, James Brendan, Camp Rucker, Ala.
Craig, John Richard, Waltham, Mass.
Croyle, Ray William, New Kensington, Pa.
da Silva, Mauricio Martins, Minneapolis.
Doores, James Ray, Galesburg, Ill.
Dopkeen, Saul Kahn, Worcester, Mass.
Drago, Rosario P., Bronx, N. Y.
Dyer, David Patterson, Grand Rapids, Mich.
Ehrlich, Leonard I., Great Neck, N. Y.
Fishler, Kenneth Orson, Salt Lake City.
Ford, Harold W., Cleveland.
Fox, Irving R., Union, N. J.
Friedenthal, Esther, Flushing, N. Y.
Gabbert, William Ries, Owensboro, Ky.
Galpin, Richard R., Birmingham, Mich.
Garben, Louis F., Jr., Glen Ridge, N. J.
Gordon, Eleanora Cunningham, Haverford, Pa.
Gould, I. Norman, Wilkes-Barre, Pa.
Grady, Roger Clifton, Detroit.
Hawes, Charles Richard, Denver.
Hodges, Richard G., Cleveland.
Hoffman, Robert Louis, Dayton, Ohio.
Huang, Erwin Ping-Shen, Montreal, Canada.
Kamakas, Nicholas C., St. Louis.
Kelsall, Charles Howard, Englewood, Colo.
Kelson, Malcolm John, Grosse Pointe Park, Mich.
Krugly, Melvin A., Chicago.
Kurnetz, Ruben, Detroit.
Lamp, Albert Leonard, Jr., Erie, Pa.
Leikin, Sanford L., Hyattsville, Md.
McClellan, Marvin R., Cincinnati.
McCormick, Glen E., Wauwatosa, Wis.
McGee, Elizabeth Lewis, Media, Pa.
Manley, Derrill Byrne, Phoenix, Ariz.
Marano, Matthew J., Newark, N. J.
Matthews, LeRoy W., Cleveland.
Mermelstein, Howard A., Pittsburgh.
Moore, Robert, Fort Meade, Md.
Nelson, Richard Stewart, Campbell, Calif.
Nicholson, Robert M., Jr., Kalamazoo, Mich.
Olsson, Gordon Quentin, Rapid City, S. Dak.
Parr, Robert L., Indianapolis.
Peirce, William H., Ann Arbor, Mich.
Pizer, Morton E., Raleigh, N. C.
Polniaszek, Mildred Jane, Chicago.
Powel, Charles C., Harrisonburg, Va.
Prec, Klara Judith, Chicago.
Raffel, William, Washington, D. C.
Rogers, Donald L., Indianapolis.
Segar, William E., Washington, D. C.
Singh, Nerissa P., Chicago.
Smith, Charles Robert, Fort Worth, Texas.
Spencer, William A., Houston, Texas.
Stockdale, Donald Karl, New York.
Tornow, W. William, Worcester, Mass.
Turnbull, Jack V., Dearborn, Mich.
Van Wyk, Judson John, Baltimore.
Wannamaker, Lewis William, Minneapolis.
Ward, Creed Francis, Cleveland.
Wedgwood, Ralph Josiah Patrick, Cleveland.
Weinberg, Samuel, Massapequa, N. Y.
Williams, Howard Jones, Jr., Macon, Ga.
Wilson, Howard Leroy, Billings, Mont.
Wright, Thomas Buerger, Waukegan, Ill.

Books

Introduction to Exceptional Children. By Harry J. Baker, Ph.D. Price, $5. Pp. 500. The Macmillan Company, 60 5th Ave., New York 11, 1953.

The increase in interest in exceptional children and their problems stimulates physicians to scrutinize literature on the subject in related professional fields to better understand how to help these children. This volume which is an "Introduction to Exceptional Children" intended for college students, primarily, unfortunately does not serve this function for physicians.

Following a brief introductory section which is concerned with a philosophy and objectives of education, there are sections on the physically handicapped, mental growth and development, neurologic and psychogenic diseases, behavior adjustments, educational retardation, and general problems. As might be anticipated in a nonmedical publication, the biological factors of concern in exceptional children are treated superficially and with unfortunate oversimplification. Discussion of educational problems does not seem to fare much better, however. Platitudinous statements also detract from the value of the book for the sophisticated reader. For example, "If we are fortunate to have normal vision, we are likely to take it for granted. The eyes serve not only to provide the sense of vision, but they also grace the countenance with individual charm." It is therefore not recommended to physicians interested in exceptional children, since its contribution would be little more than the presentation of an outline of problems which these children face.

Illustrated Review of Fracture Treatment. By Frederick Lee Liebolt. Price, $4. Pp. 229, with 605 illustrations. Lange Medical Publications, University Medical Publishers, Box 1215, Los Altos, Calif., 1954.

In this review of fracture treatment, which the author has intended for use by the medical student, house officer, and general practitioner, we find material which should be very useful to the medical student and the teacher alike as an outline to follow in teaching a course in fractures. The book is not exhaustive and would not be adequate to take the place of larger texts but is, nevertheless, well illustrated and nicely organized. The author has attempted to be brief, and in a few instances I believe valuable information has been omitted which perhaps could be added in future editions. For instance, the author does not stress the difference in treatment in the aged person with the compression fracture of the spine or the impacted fracture of the surgical neck of the humerus from the treatment of such injuries in young people, and the general practitioner using this volume as his guide might well need this information.

The generally accepted teachings of fractures are well covered in this volume, but the controversial material and some of the more radical types of treatment are either omitted or dealt with very briefly. In a book of this type, I feel that this is proper, as these matters will be clarified and enlarged upon by the teacher.

While this book is not a suitable volume to be used as a reference book, it has a real field of usefulness as an outline review of fractures and their treatment.

Auditory Disorders in Children. By Helmer R. Myklebust. Price, $6. Pp. 367. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1954.

This manual deals with the complex problem of auditory and speech disorders, chiefly in children aged 1 to 6 years. Part I introduces the problem of auditory disorders and language development. Part II interprets the child's history. Part III evaluates the behavior symptomatology. Part IV gives the technique of examination. Part V outlines recommended procedures. Of 228 children referred in one year, 45% were deaf from ear deficiencies and 55% had emotional, aphasic, or mental deficiencies. Differentiation is accomplished by referrals to pediatrician, otolaryngologist, psychiatrist, and educator. The chapter summaries help to coordinate the content rapidly. Some of the summary discussion should be in the text. Individual chapters on peripheral deafness, aphasia, psychic deafness, and mental deficiency are very informative. The chapter on auditory capacity examination is very practical. The chapter on psychological examination rates the peripherally deaf nearest normal, then the psychologically deaf, the aphasic, and the mentally deficient. Case studies are included. The book is well written and offers much helpful information for those who work with children having speech and hearing defects.

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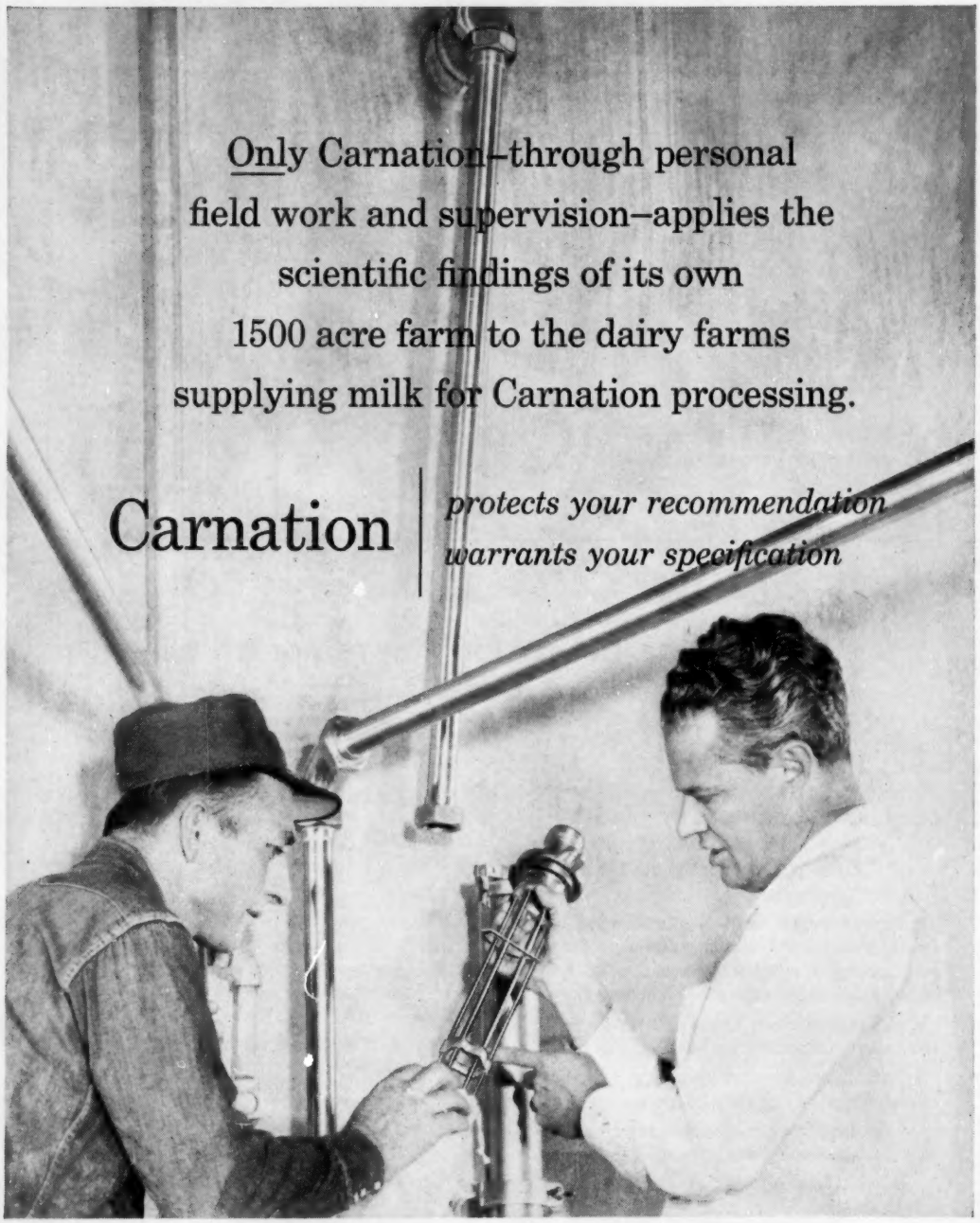
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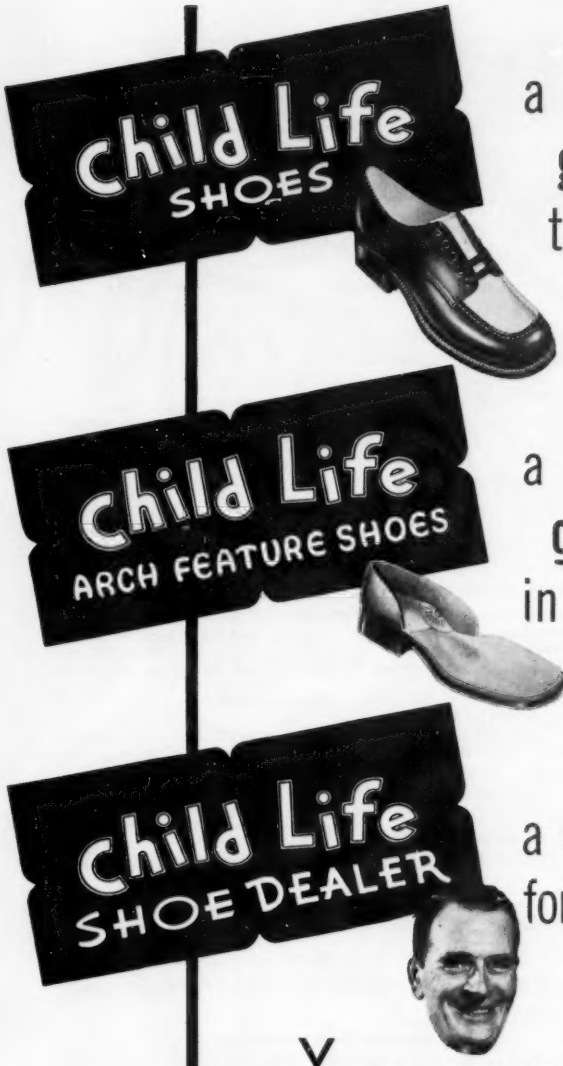

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1. Editorial: J.A.M.A. *134*:606 (June 14) 1947. **2.** Hansen, A. E., and Burr, G. O.: J.A.M.A. *132*:855 (Dec. 7) 1946. **3.** Hansen, A. E.; Knott, E. M.; Wiese, H. F.; Shaperman, E., and McQuarrie, I.: Am. J. Dis. Child. *73*:1 (Jan.) 1947. **4.** Hansen, A. E.: In, Vitamin B6 in Human Nutrition, Report of the Tenth M & R Pediatric Research Conference, Columbus, M & R Laboratories, 1954, p. 51. **5.** National Research Council: Maternal Nutrition and Child Health, Bull. 123 (Nov.) 1950. **6.** Meyer, H. F.: Essentials of Infant Feeding for Physicians, Springfield, Illinois, Charles C. Thomas, 1952, p. 44. **7.** Martin, C. W.: New York State J. Med. *32*:1012 (Sept.) 1932. **8.** Stoesser, A. V., and Nelson, L. S.: Journal Lancet *73*:487 (Dec.) 1953.

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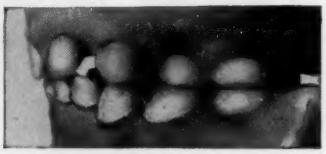

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Since they deal with the biologic value of proteins and with the vulnerability of children to inadequate protein intake, the following statements accompanying the Board's recent announcement of protein allowances merit attention:

> "The nutritive value of proteins is primarily dependent on the amino acid composition, and the lower biological value of vegetable proteins as compared with animal proteins is well known. The inclusion of a variety of foods, and especially products of animal origin, in the diet assures a satisfactory amino acid distribution as well as sources of other nutrients . . . Recent wide-spread interest in protein deficiency syndromes such as Kwashiorkor disease[2] emphasizes the particular vulnerability of children who receive diets in which the protein content is low and primarily of vegetable origin, even when the total calorie intake is adequate or high."[1]

Meat, when cooked, presents approximately 25 to 30 per cent of high quality protein, easily digested and readily assimilable. Meat is especially acceptable to children and should be a regular item of their diets.[3] It also provides valuable amounts of B vitamins and essential minerals.

Recommended Daily Protein Allowances[1]

Children	*Protein*	Boys	*Protein*
1-3 yrs., 27 lb., 34 in.	40 Gm.	10-12 yrs., 78 lb., 57 in.	70 Gm.
4-6 yrs., 40 lb., 43 in.	50 Gm.	13-15 yrs., 108 lb., 64 in.	85 Gm.
7-9 yrs., 59 lb., 51 in.	60 Gm.	16-20 yrs., 139 lb., 69 in.	100 Gm.
Girls		**Men**	
10-12 yrs., 79 lb., 57 in.	70 Gm.	25-65 yrs., 143 lb., 67 in.	65 Gm.
13-15 yrs., 108 lb., 63 in.	80 Gm.	**Women**	
16-20 yrs., 120 lb., 64 in.	75 Gm.	25-65 yrs., 121 lb., 62 in.	55 Gm.

1. Recommended Dietary Allowances, Report of the Food and Nutrition Board, National Academy of Sciences—National Research Council, Publication 302, Washington, D.C., 1953.
2. Brock, J. F., and Autret, M.: Kwashiorkor in Africa, Bull. World Health Organ. *5*:1 (1952).
3. McLester, J. S., and Darby, W. T.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, p. 218.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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(1) National Research Council, "Recommended Dietary Allowances," reprint 129 (1948)

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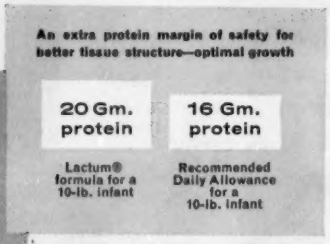
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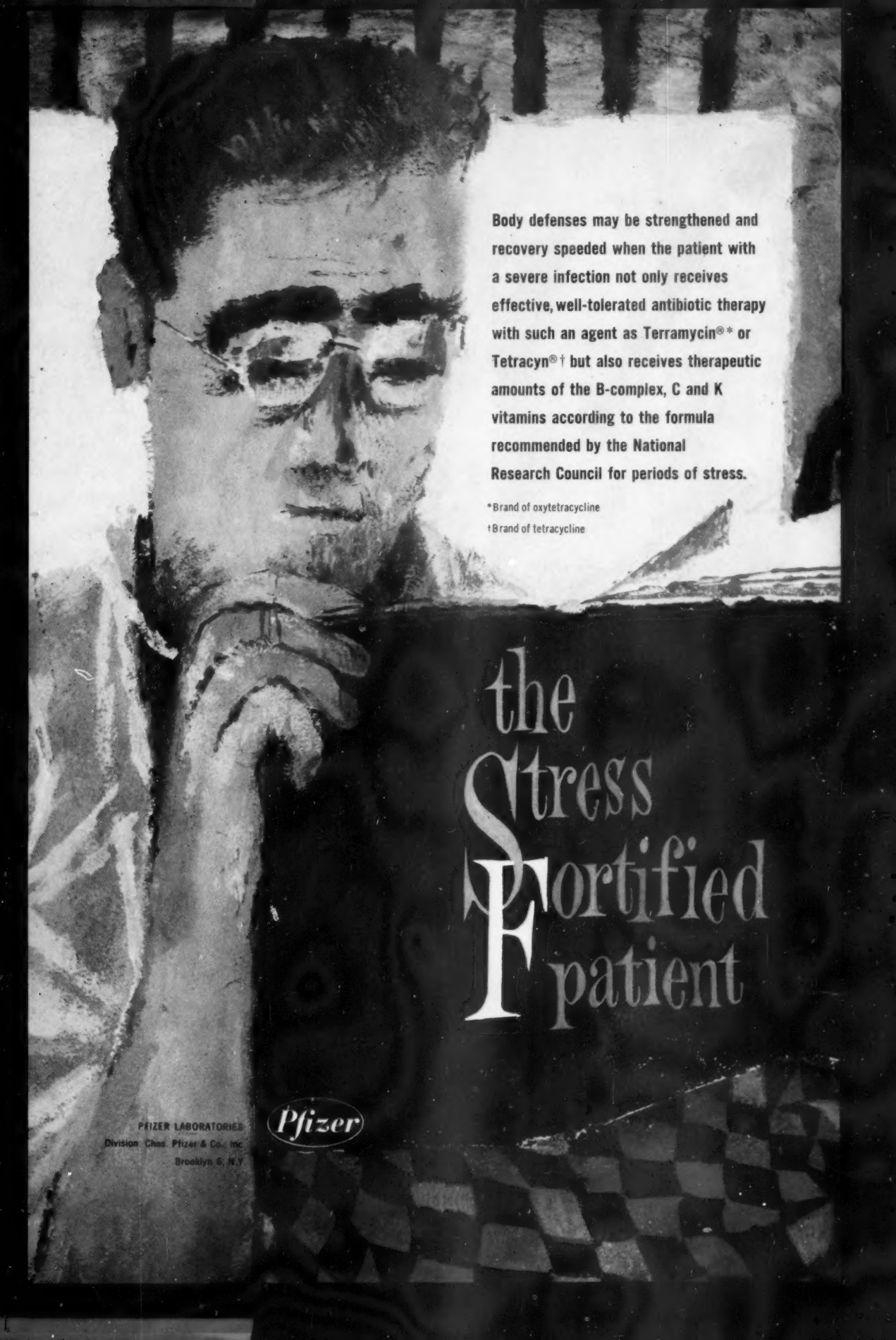
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